CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74928

BIOEQUIVALENCE REVIEW(S)

JAN 31 1997

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Nicardipine HCl
20 and 30 mg Capsules
ANDA #**74-928**
Reviewer: Z.Z. Wahba
WP #74928sdw.696

Genpharm Inc.
Toronto, Canada
Submission Date:
July 16, 1996
January 06, 1997
October 23, 1996

REVIEW OF TWO IN-VIVO BIOEQUIVALENCE STUDY, IN VITRO DISSOLUTION TESTING DATA AND A WAIVER REQUEST

I. OBJECTIVE:

To review the following:

1. Genpharm's in vivo bioequivalence study under fasting and non-fasting conditions comparing its 30 mg strength Nicardipine HCl Capsules to the reference drug product, Cardene® 30 mg Capsules manufactured by Syntex.

2. Dissolution data for 20 mg and 30 mg strengths for the test and reference drug products.

3. Waiver request for the 20 mg strength capsules.

II. INTRODUCTION:

Nicardipine is a calcium channel blocker agent which inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle without changing serum calcium concentrations. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells' specific channels. The effects of nicardipine are more selective to vascular smooth muscle than cardiac muscle.

Nicardipine is completely absorbed following oral doses administered as capsules. The levels are detectable as early as 20 minutes following an oral dose and maximum levels are observed within 30 minutes to 2.0 hours (the average T_{max} mean = 1.0 hour). The pharmacokinetics of the nicardipine are nonlinear due to saturable hepatic first pass metabolism. Its systemic bioavailability is about 35% following a 30 mg oral dose at steady state due to the saturable hepatic first pass metabolism. Increasing doses result in a disproportionate increase in plasma levels. Because nicardipine is extensively metabolized by the liver, the plasma levels of the drug are influenced by changes in hepatic function.

Nicardipine plasma levels were higher in patients with severe liver disease than in normal subjects. Studies showed that when

nicardipine was administered one or three hours after a high fat meal, the AUC and C_{max} means were lower 20% to 30% than when the drug was given under fasting conditions. Elimination over the first 8 hours after dosing is much faster with a $T_{\frac{1}{2}}$ of 2-4 hours. Nicardipine is highly protein bound (more than 95%) in human plasma over a wide concentration range.

Nicardipine HCl (Cardene®) is available in 20 mg and 30 mg capsules for use in cases of hypertension and angina. The recommended dosage is 20 to 40 mg three times a day.

III. BIOEQUIVALENCE STUDY UNDER FASTING CONDITION
Clinical Study #EP131

A. Sponsor:

Genpharm Pharmaceuticals
37 Advance Road
Etobicoke, Ontario M8Z 2S6

Clinical Study Dates:
12/13/1995 and 12/20/1995

Analytical Study Dates:
01/04/1996 to 02/27/1996

B. Study design:

Single dose, randomized, two-way crossover study under fasting conditions.

C. Subjects:

Thirty three (33) healthy male subjects were enrolled and completed the study (subjects #1-33). The subjects were in the range of 20 to 45 years of age, and their body weights were within ± 15% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

Subject Selection Criteria:
Only medically and physically healthy subjects with clinically

normal ranges of laboratory tests (blood chemistry, hematology, urinalysis) were enrolled in the study.

Subject Exclusion Criteria:

- A history of cardiovascular, gastrointestinal, renal, hepatic, pulmonary, neurological or hematological disease.
- A history of chronic alcohol or drug addiction.
- A history of allergic responses to the class of drug being tested.
- Use of tobacco in any form.
- Blood donation within the past 20 weeks prior to the study.
- Use of any investigational drug within 30 days preceding entry into the study.

Subject Restrictions:

- No subject took any medications, including OTC products for at least 2 weeks prior to the beginning of the study and until completion of the study.
- No alcoholic, xanthine and caffeine containing foods and beverages were allowed, beginning with 24 hours prior to dosing and until completion of the study.

D. Food and Fluid Intake:

Subjects fasted overnight for at least 10 hours before dosing and 4 hours after dosing. Water was not permitted for 2 hours after the dose, but was allowed at all other times. The subjects received their medication with 240 mL of water according to randomized dosing schedule. Standard meals were provided at appropriate times thereafter.

E. Treatment:

Test product: 1 X 30 mg Nicardipine HCl Capsule (Genpharm), Package Lot #101908, Bulk Lot #101501, Batch size (not given), assay potency (not given), content uniformity (not given), Packaging date: Oct. 23, 1995.

Reference product: 1 X 30 mg Cardene® Capsule (Syntex), Lot #04860, assay potency (not given), content uniformity (not given), expiration date: 08/1997.

Washout period: 7 days.
A single 30 mg dose was given in each period of the study.

F. Subject Monitoring:

Vital signs (blood pressure and heart rates) were monitored at 1, 2, 3 and 4 hours post-dose and at the discretion of the clinical investigators. There were no clinically significant

changes noted in vital sign measurements.

G. **Blood Sampling**:

Blood samples were collected in vacutainers with EDTA, before dosing (2X20 mL) and at 0.25, 0.50, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 16 and 24 hours post-dosing (1x10 mL each). The total volume of blood drawn from each subject did not exceed 526 mL. The plasma samples were separated, collected and stored frozen at -20°C or lower until analysis.

H. **Assay Methodology**:

I. **Protocol Deviations**:

There were a number of deviations from the protocol. The deviations were mainly dealt with some subjects who consumed OTC products, vitamins or caffeine containing beverages prior to the beginning the study. The deviations were judged unlikly to affect the pharmacokinetics of nicardipine (vol. C1.4, p 1215 &1216).

I. **Adverse Events**:

The adverse reactions have been reported (vol. C1.4, p #1219-1221). All adverse reactions (headache, lightheaded,

nurvousness and blurred vision) were considered mild cases. No medication was required for any medical events. No subject was discontinued from the study due to an adverse reaction.

J. **Data Analysis**:

Thirty three (33) healthy male subjects were enrolled and completed the study (subjects #1-33). The pharmacokinetic parameters of nicardipine were analyzed using SAS (GLM procedure) for analysis of variance. The pharmacokinetic parameters of the plasma nicardipine concentrations, as well as the following parameters, AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ are summarized in Tables #3-5.

Table 3
Mean Plasma Concentrations of Nicardipine in 33 Subjects Following 30 mg Oral Doses of Nicardipine Under Fasting Conditions
Unit: pg/mL

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	163.97	427.56	288.70	786.85	0.57
0.5	27028.94	27965.44	22873.45	21804.49	1.18
0.75	43991.66	30182.60	45486.00	30196.47	0.97
1	40859.38	21849.34	40590.06	23123.70	1.01
1.33	35058.78	20015.03	30739.27	12473.67	1.14
1.67	25567.84	14287.08	22682.12	9833.61	1.13
2	20168.88	14530.00	17783.45	8868.46	1.13
2.5	14040.63	12500.40	12478.48	7875.45	1.13
3	9990.34	7728.43	8881.24	5346.12	1.12
4	5244.75	2761.92	5105.06	2381.14	1.03
6	2397.88	1308.86	1983.64	888.56	1.21
8	1397.16	805.56	1279.61	690.81	1.09
12	666.31	562.57	565.88	539.40	1.18
16	288.46	484.99	268.18	372.29	1.08
24	101.59	274.77	145.06	261.97	0.70

MEAN1=Test MEAN2=Reference RMEAN12=T/R ratio

Table 4
Summary of Pharmacokinetic Parameters in 33 Subjects Following 30 mg Oral Doses of Nicardipine Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	97448.66	49990.59	88232.94	34497.95	1.10
AUCT	92953.01	47643.37	85887.42	33850.89	1.08
CMAX	54121.47	29938.59	52436.00	25171.74	1.03
KE	0.28	0.12	0.30	0.16	0.94
*LAUCI	87333.60	0.46	82234.85	0.38	1.06
*LAUCT	83378.31	0.46	79941.16	0.38	1.04
*LCMAX	47762.06	0.49	47774.91	0.43	1.00
THALF	3.18	1.92	3.61	2.82	0.88
TMAX	0.93	0.34	0.95	0.37	0.99

UNIT: AUC=PG HR/ML CMAX=PG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table 5
LSMeans and 90% Confidence Intervals (Under Fasting Conditions)

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	96358.43	90694.50	90.54	121.95
AUCT	92067.64	85860.44	92.46	122.00
CMAX	53529.02	52520.18	88.63	115.21
*LAUCI	86327.09	84682.23	88.40	117.56
*LAUCT	82526.48	79903.80	90.42	117.97
*LCMAX	47181.55	47846.91	87.57	111.04

UNIT: AUC=PG HR/ML CMAX=PG/ML
Low CI 12=Lower C.I. for T/R UPP CI 12=Upper C.I. for T/R
* The values represent the LSMEANS (antilog of the means of the logs).

Table 6
Test/Reference Products Ratios
for Pharmacokinetic Parameters for Individual Subjects
(Under Fasting Conditions)

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	2						
2	2	1						
3	3	2						
4	4	1						
5	5	1						
6	6	2						
7	7	1						
8	8	2						
9	9	2						
10	10	1						
11	11	1						
12	12	2						
13	13	2						
14	14	2						
15	15	1						
16	16	1						
17	17	2						
18	18	1						
19	19	2						
20	20	1						
21	21	2						
22	22	2						
23	23	1						
24	24	1						
25	25	1						
26	26	2						
27	27	2						
28	28	1						
29	29	2						
30	30	1						
31	31	1						
32	32	2						
33	33	2						

1=Test product 2=Reference product

Table 7
Summary of Mean and SD of Individual T/R Ratios
(Under Fasting Conditions)

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	32	1.14	0.57	0.44	3.26
RAUCI12	29	1.13	0.57	0.44	3.19
RCMAX12	32	1.08	0.50	0.49	2.86
RTMAX12	32	1.07	0.50	0.38	2.60
RKE12	29	1.26	0.97	0.53	5.80
RTHALF12	29	1.01	0.39	0.17	1.87

1. The mean plasma nicardipine levels reached a maximum level of

concentration around 0.75 hour (Table #3 and the attached Figures #1 and #2).

2. The 90% confidence intervals for the log-transformed AUC_{0-t}, AUC_{0-inf} and C_{max} were within the acceptable range of 80-125% (Table #5). The geometric T/R mean ratios for AUC_{0-t}, AUC_{0-inf} and C_{max} were 1.04, 1.06 and 1.00, respectively (Table #4).

   There were no significant sequence, period or treatment effects of the test and reference drug treatments for the log-transformed pharmacokinetic parameters AUC_{0-t} and $AUC_{0-\infty}$.

   For the C_{max}, there were no significant sequence and treatment effects of the test and reference drug treatments. However, there was a significant period effect (p less than 0.05) for the log-transformed pharmacokinetic parameter C_{max}.

3. The arithmetic T/R mean ratios for T_{max}, K_{el} and $T_{1/2}$ were 0.99, 0.94 and 0.88, respectively (Table #4).

IV. BIOEQUIVALENCE STUDY UNDER NON-FASTING CONDITIONS (clinical study project #EP143)

A. Sponsor:

Genpharm Pharmaceuticals
37 Advance Road
Etobicoke, Ontario M8Z 2S6

Clinical Study Dates:
Period I: December 02, 1995
Period II: December 09, 1995
Period III: December 16, 1995

Analytical Study Dates:
04/18/1996 to 05/14/1996

B. Study design:

Randomized, three-way crossover, single dose study, under fasting and non-fasting conditions.

C. **Subjects**:

Eighteen (18) healthy male subjects were initially dosed in this study but only 15 subjects (#1-10, 12-14 and #16-17) completed the clinical study. Subject #11 and #18 elected to withdraw due to flu and employment respectively. Subject #15 was discontinued post period 2 due to maximum blood volume. The firm has mentioned that subject #15 was not eligible for project #EP143 in accordance with volunteer policy and was thus withdrawn from the study (vol. C1.1, p #161).

Subject Exclusion Criteria:
Same as in Protocol #EP131.

Subject Restrictions:
Same as in Protocol #EP131.

D. **Treatment**:

Test Product:

Treatment A: 1 X 30 mg Nicardipine HCl Capsule (Genpharm), Package Lot #101908, Bulk Lot #101501, Batch size (not given), assay potency (not given), content uniformity (not given), Packaging date: Oct. 23, 1995, under fasting conditions.

Treatment B: 1 X 30 mg Nicardipine HCl Capsule (Genpharm), Package Lot #101908, Bulk Lot #101501, Batch size (not given), assay potency (not given), content uniformity (not given), Packaging date: Oct. 23, 1995, under non-fasting conditions.

Reference Product:

Treatment C: 1 X 30 mg Cardene® Capsule (Syntex), Lot #04860, assay potency (not given), content uniformity (not given), expiration date: 08/1997, under non-fasting conditions.

Treatment Sequence: ABC, BCA, CAB

Washout period: 7 days
A single 30 mg dose was given in each period of the study.

E. **Drug, Food and Fluid Intake**:

Subjects who received treatment A, fasted overnight for 10 hours before dosing and for 4 hours after drug administration. Subjects who were fed standard recommended breakfast prior to dosing (treatments B and C) only fasted for 9.5 hours. Treatments B and C differed from treatment A in that the subjects were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug

administration. The standard breakfast meal contained the following: one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hashed brown potatoes, eight fluid ounces (240 ml) of whole milk and six fluid ounces (180 ml) of orange juice. Each dose was followed by 8 fluid ounces (240 mL) of room temperature tap water according to randomized dosing schedule. Water was permitted ad lib until 2 hours before dosing and again at 4 hours after dosing. Standard meals were provided at appropriate times thereafter.

F. Subject Monitoring:

Vital signs (blood pressure and heart rates) were monitored at 1, 2, 3, and 4 hours post-dose and at the discretion of the clinical investigators. There were no clinically significant changes noted in vital sign measurements (vol. C1.1, p #164).

G. Protocol Deviations:

There were a number of deviations from the protocol. The deviations were mainly due to late check in to the clinic, delay in collecting four samples (the deviations were 2-8 minutes), consumption OTC products and vitamins. The deviations were judged unlikly to affect the biostudy (vol. C1.1, p 164-165).

H. Assay Methodology:

I. **Blood sampling**:

Blood samples were collected in vacutainers with EDTA, before dosing (2X20 mL) and at 0.25, 0.50, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 16 and 24 hours post-dosing (1x10 mL each). The total volume of blood drawn from each subject did not exceed 526 mL. The plasma samples were

separated, collected and stored frozen at -20°C or lower until analysis.

J. **Adverse Events**:

The adverse reactions have been reported (vol. C1.1, p #167). There were no serious adverse events or any events which required terminating any subjects from the study.

K. **In Vivo Results**:

Eighteen (18) healthy male subjects were initially dosed in this study but only 15 subjects (#1-10, 12-14 and #16-17) completed the clinical study. Subject #11 and #18 elected to withdraw due to flu and employment respectively. Subject #15 was discontinued post period 2 due to maximum blood volume. The firm has mentioned that subject #15 was not eligible for project #EP143 in accordance with volunteer policy and was thus withdrawn from the study (vol. C1.1, p #161). The pharmacokinetic parameters of the plasma concentrations of nicardipine are summarized in the tables below:

Table 10
Mean Plasma Concentrations of Nicardipine (pg/mL) in 15 Subjects Following 30 mg Oral Doses of Nicardipine Under Non-Fasting Conditions

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.25	234.57	469.01	0.00	0.00	0.00	0.00
0.5	16694.50	20040.34	42.93	166.28	113.80	325.84
0.75	36533.07	25700.76	774.87	1366.75	1008.27	1702.25
1	36260.36	26147.02	1991.47	3209.12	2145.87	3502.67
1.33	30103.64	23211.42	5489.33	7392.86	4129.33	4585.93
1.67	23887.00	17405.01	7559.73	7639.48	7008.40	5875.99
2	18314.07	9856.08	10870.20	7389.21	10524.93	6755.56
2.5	12317.57	6167.47	15117.87	7901.22	13036.60	7492.19
3	9018.57	4294.62	14912.27	7384.97	12589.40	6872.12
4	5025.86	2168.48	9422.80	3286.56	8497.27	3159.77
6	1703.71	702.31	2148.07	521.52	2105.93	872.30
8	974.07	565.98	1073.00	320.33	1117.13	464.34
12	254.71	370.29	167.53	288.11	258.80	331.33
16	39.14	146.46	0.00	0.00	0.00	0.00
24	0.00	0.00	0.00	0.00	0.00	0.00

(CONTINUED)

TIME HR	RMEAN12	RMEAN13	RMEAN23
0	.	.	.
0.25	.	.	.
0.5	388.85	146.70	0.38
0.75	47.15	36.23	0.77
1	18.21	16.90	0.93
1.33	5.48	7.29	1.33
1.67	3.16	3.41	1.08
2	1.68	1.74	1.03
2.5	0.81	0.94	1.16
3	0.60	0.72	1.18
4	0.53	0.59	1.11
6	0.79	0.81	1.02
8	0.91	0.87	0.96
12	1.52	0.98	0.65
16	.	.	.
24	.	.	.

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 11
Summary of Pharmacokinetic Parameters in 15 Subjects Following 30 mg Oral Doses of Nicardipine Under Non-Fasting Conditions

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
AUCI	78076.02	42709.47	50777.95	22706.26	50485.01	17473.17
AUCT	76077.51	42308.61	48977.75	22615.45	44780.09	19041.76
CMAX	44123.36	27000.08	16245.47	8350.77	14898.27	6887.17
KE	0.42	0.13	0.49	0.09	0.45	0.10
*LAUCI	69767.30	0.47	46129.95	0.46	47640.96	0.36
*LAUCT	67791.43	0.48	44241.39	0.47	40849.82	0.46
*LCMAX	38158.27	0.55	14193.83	0.56	13295.69	0.52
THALF	1.83	0.65	1.47	0.30	1.62	0.36
TMAX	1.02	0.40	2.74	0.38	2.87	0.67

(CONTINUED)

PARAMETER	RMEAN12	RMEAN13	RMEAN23
AUCI	1.54	1.55	1.01
AUCT	1.55	1.70	1.09
CMAX	2.72	2.96	1.09
KE	0.86	0.94	1.10
*LAUCI	1.51	1.46	0.97
*LAUCT	1.53	1.66	1.08
*LCMAX	2.69	2.87	1.07
THALF	1.25	1.13	0.90
TMAX	0.37	0.36	0.96

1=Test-Fast 2=Test-NonFast 3=Ref.-NonFast
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR THALF=HR KE=1/HR
* The values represent the geometric means (antilog of the means of the logs).

Table #12
T/R Values for Individual Subjects
(Under Non-Fasting Conditions)

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12	RAUCT13	RAUCI13	RCMAX13
1	1	1									
2	2	2									
3	3	3									
4	4	2									
5	5	3									
6	6	1									
7	7	3									
8	8	1									
9	9	2									
10	10	3									
11	12	2									
12	13	1									
13	14	2									
14	16	3									
15	17	1									

OBS	RTMAX13	RKE13	RTHALF13	RAUCT23	RAUCI23	RCMAX23	RTMAX23	RKE23	RTHALF23
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
11									
12									
13									
14									
15									

Table 13

Summary of Mean and SD of Individual T/R Ratios (Under Non-Fasting Conditions)

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	14	1.65	0.70	0.88	3.55
RAUCI12	14	1.62	0.66	0.87	3.39
RCMAX12	14	2.89	1.04	1.54	4.82
RTMAX12	14	0.37	0.12	0.25	0.67
RKE12	14	0.84	0.19	0.33	1.17
RTHALF12	14	1.30	0.53	0.85	3.06
RAUCT13	14	1.77	0.47	0.92	2.46
RAUCI13	12	1.69	0.47	0.90	2.42
RCMAX13	14	3.16	1.11	1.31	5.50
RTMAX13	14	0.37	0.17	0.19	0.84
RKE13	12	0.85	0.20	0.53	1.15
RTHALF13	12	1.24	0.33	0.87	1.88
RAUCT23	15	1.12	0.30	0.56	1.59
RAUCI23	13	1.10	0.28	0.57	1.58
RCMAX23	15	1.12	0.37	0.65	1.78
RTMAX23	15	1.00	0.24	0.67	1.50
RKE23	13	1.11	0.29	0.65	1.72
RTHALF23	13	0.96	0.25	0.59	1.53

1. Under non-fasting conditions, the mean plasma nicardipine levels reached the maximum around 2.5 hours (Table #10 and Figures #3 and #4). The absorption rate for the test product under non-fasting conditions was slower compared to the test product under fasting conditions. In general, the results show a significant food effect on the mean plasma levels as well as the pharmacokinetic parameters of nicardipine when the drug was given with food.

2. Under non-fasting conditions, the ratios of the test mean to the reference mean (RMEAN2/3) for the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were all within the acceptable range of 0.8 to 1.2 (Table #11).

V. FORMULATION COMPARISON

Genpharm's comparative formulations for its drug product, Nicardipine, 20 mg and 30 mg capsules are summarized in Table #10.
The reference product, Syntex's Cardene® Capsule contains the following: nicardipine HCl, magnesium stearate and pregelatinized Starch.

Table 14
Formulation Comparison
(Should not be released under FOI)

Ingredients	20 mg Capsules		30 mg Capsules	
	mg/capsule	%	mg/capsule	%
Nicardipine HCl	20.0	12.5	30.0	12.5
Pregelatinized Starch NF				
Magnesium Stearate NF				
Total Capsule fill weight	160.00 mg		240.00 mg	
Capsule#3 White opaque `0041' /light blue opaque `G'	X	X	N/A	N/A
Capsule #2 light blue opaque `0042'/Light blue opaque `G'	N/A	N/A	X	X

X= Excipient present in formulation
N/A= Not applicable

The 20 mg strength of the test product is proportionally similar in its active and inactive ingredients to the 30 mg strength which went under the current bio-study.

V. **IN VITRO DISSOLUTION TESTING**:

The firm has determined dissolution of the test products in 900 mL of 0.1N HCl, instead of 0.0333M citrate buffer (pH 4.5) recommended by the Division of Bioequivalence. Therefore, dissolution testing performed by the sponsor does not meet Agency specifications (see the deficiency section).
Note: There is no USP dissolution testing procedure specified for nicardipine hydrochloride capsules.

VI. **COMMENTS**:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Genpharm's Nicardipine HCl Capsules 30 mg and the reference product, Syntex's Cardene® Capsules 30 mg are

bioequivalent. The 90% confidence intervals for the log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were all within the acceptable range of 80-125%. However, the ANDA has been found incomplete by the Division of Bioequivalence for the reasons cited in the deficiency section (see below).

2. Under non-fasting conditions: The in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Genpharm's Nicardipine HCl Capsules 30 mg is bioequivalent to the reference product, Syntex's Cardene® Capsules 30 mg. The ratios of the test mean to the reference mean for the AUC_{0-t}, $AUC_{0-\infty}$ C_{max} were within the acceptable range of 0.8 to 1.2. The results show a significant food effect on the mean plasma levels as well as the pharmacokinetics parameters of nicardipine when the drug is given with food. However, the ANDA has been found incomplete by the Division of Bioequivalence for the reasons cited in the deficiency section (see below).

VII. **DEFICIENCIES**:

1. Dissolution testing conducted by Genpharm Inc. on its nicardipine hydrochloride 20 mg and 30 mg capsules does not meet the agency specifications. The firm has determined dissolution of the test products in 900 mL of 0.1N HCl, instead of 0.0333M citrate buffer (pH 4.5) recommended by the Division of Bioequivalence. There is no USP dissolution testing procedure specified for nicardipine hydrochloride capsules.
Therefore, the sponsor should conduct dissolution testing following the Agency specifications.

   The firm should conduct the dissolution testing for both strengths, 20 and 30 mg using USP 23 apparatus 2 (paddles) at 50 rpm in 900 mL of 0.0333M citrate buffer (pH 4.5), The dissolution testing should meet the following specifications:

   > Not less than of the labeled amount of the drug product in the capsule is dissolved in 30 minutes.

   The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot number of the dissolution testing should be identical to the one used in the in vivo bioeqivalence study.

2. The firm should submit information on the lot/batch size of the test product, as well as the assay potency and content uniformity data for the test and reference products.

VIII. RECOMMENDATION

1. The two in vivo bioequivalence studies (single-dose under fasting and single-dose non-fasting) conducted by Genpharm Inc. on its Nicardipine Hydrochloride 30 mg Capsule, lot #101908, comparing it to the reference product Cardene® 30 mg Capsule, lot #04860, manufactured by Syntex Laboratories, have been found to be acceptable to the Division of Bioequivalence. The two studies demonstrate that under fasting and non-fasting conditions, Genpharm's Nicardipine Hydrochloride 30 mg Capsules are bioequivalent to Cardene® 30 mg Capsules, manufactured by Syntex Laboratories. However, the application is incomplete.

2. From the bioequivalence stand point the sponsor has not met requirements of in vitro dissolution testing. The sponsor should be informed of deficiencies #1 and #2 as well as the recommendation.

3. Sponsor's request for the waiver of in vivo bioequivalence requirements for its Nicardipine Hydrochloride 20 mg capsules will be reviewed upon receipt of acceptable dissolution data on its 20 mg and 30 mg Nicardipine Hydrochloride Capsules.

4. The in vitro dissolution testing conducted by Genpharm Inc. on its Nicardipine Hydrochloride 20 mg and 30 mg capsules is not acceptable. The firm should conduct dissolution testing using USP 23 apparatus 2 (paddles) at 50 rpm in 900 mL of 0.0333M citrate buffer (pH 4.5), instead of 0.1N HCl. The dissolution testing should meet the following specifications:

   Not less than of the labeled amount of the drug product in the capsule is dissolved in 30 minutes.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRF
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1/23/97

Concur: _____ Date: 1/31/97

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

ANDA 74-928

AUG 18 1997

Lipha Pharmaceuticals Inc.
U.S. Agent for: Genpharm Inc.
Attention: Anita M. Goodman, M.D.
9 West 57 th 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 Nicardipine Hydrochloride Capsules, 20 mg and 30 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 using the following method: 900 mL 0.0333 M Citrate buffer pH 4.5 at 37°C applying USP 23 Apparatus II (Paddle) at 50 rpm, and

   The test product should meet the following specifications:

   Not less than of the labeled amount of the drug product in the Capsule 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,

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

AUG - 1 1997

Nicardipine HCl
20 and 30 mg Capsules
ANDA #**74-928**
Reviewer: Z.Z. Wahba
WP #74928a.397

Genpharm Inc.
Toronto, Canada
Submission Date:
March 12, 1997
June 25, 1997

AMENDMENT TO A REVIEWED IN VIVO BIOEQUIVALENCE STUDY AND DISSOLUTION DATA
(Dated January 31, 1997)

BACKGROUND

The firm had previously submitted an in vivo bioequivalence study (single dose) under fasting and non-fasting conditions comparing its 30 mg strength Nicardipine HCl Capsules to the reference drug product, Syntex's Cardene® 30 mg Capsules.

The submission was reviewed and was found incomplete by the Division of Bioequivalence (review dated Jan. 31, 1997, ANDA #74-928) due to problems cited in the deficiency comments.

In this submission, the firm has responded to the deficiency comments with additional information.

Deficiency Comment #1

Dissolution testing conducted by Genpharm Inc. on its nicardipine hydrochloride 20 mg and 30 mg capsules does not meet the agency specifications. The firm has determined dissolution of the test products in 900 mL of 0.1N HCl, instead of 0.0333M citrate buffer (pH 4.5) recommended by the Division of Bioequivalence. There is no USP dissolution testing procedure specified for nicardipine hydrochloride capsules. Therefore, the sponsor should conduct dissolution testing following the Agency specifications.

The firm should conduct the dissolution testing for both strengths, 20 and 30 mg using USP 23 apparatus 2 (paddles) at 50 rpm in 900 mL of 0.0333M citrate buffer (pH 4.5), The dissolution testing should meet the following specifications:

Not less than of the labeled amount of the drug product in the capsule is dissolved in 30 minutes.

The dissolution should be conducted for both the test and reference products, performed simultaneously. The lot number of the dissolution testing should be identical to the one used in the in vivo bioeqivalence study.

The firm's response to comment #1

Method: USP 23 apparatus II (Paddle) at 50 rpm
Medium: 900 mL of 0.0333 M Citrate buffer (pH 4.5)
Temperature: 37°C ± 0.5°C
No. Units Tested: 12
Sampling Time: 5, 10, 15, 20 and 30 minutes
Methodology:
Specification: NLT (Q) is dissolved in 30 minutes
Test Product: Genpharm's Nicardipine HCl Capsules 20 mg and 30 mg.
30 mg Capsule, Bulk lot#101501, Package Lot#101905
20 mg Capsule, Bulk lot#101502, Package Lot#101910

Reference Product: Syntex' Cardene® Capsules, 20 mg and 30 mg.
30 mg Capsule, Lot#04860
20 mg Capsule, Lot#B0276

Note: The firm's in vivo bioequivalence study (for 30 mg strength) was conducted using capsules from the Bulk Lot #101501, Package Lot #101908. The dissolution testing was conducted on the Bulk Lot #101501, Package Lot #101905. Difference in package lot number is due to the fact that the firm divided the bulk lot into packages with different lot numbers as the following: bottles of 100 (Lot #101908), bottles of 500 (Lot #101909) and blister of 10 (Lot #101905). Since both the bulk lot numbers of the dissolution testing capsules and the capsules that were used in the bioequivalence study are identical, the dissolution on the bio-lot is acceptable.

The dissolution testing results are presented in Table #1.

Table 1. In Vitro Dissolution Testing
Drug (Generic Name): Nicardipine HCl Dose Strength: 20 mg and 30 mg ANDA No.:74-928 Firm: Genpharm Inc. Submission Date: July 16, 1996 File Name: 74928a.397
I. Conditions for Dissolution Testing:
USP 23 Basket: Paddle:X RPM: 50 No. Units Tested: 12 Capsules Medium: 900 mL of 0.0333M (pH 4.5) Specifications: NLT of the labeled amounts of nicardipine is dissolved in 30 minutes. Reference Drug: Syntex's Cardene® Capsules, 20 mg and 30 mg Assay Methodology:

II. Results of In Vitro Dissolution Testing: Nicardipine						
Sampling Times (min)	Test Product: Nicardipine Bulk Lot # 101501 Strength(mg) 30			Ref. Product: Nicardipine Lot # 04860 Strength(mg) 30		
	Mean %	Range	%CV	Mean %	Range	%CV
5	15.7		40.35	19.8		44.81
10	85.9		7.10	80.6		8.31
15	101.5		1.93	99.5		3.21
20	103.2		2.13	101.9		3.11
30	102.8		2.10	101.8		3.411
Sampling Times (min)	Test Product: Nicardipine Bulk Lot #101502 Strength(mg) 20			Ref. Product: Nicardipine Lot #B0276 Strength(mg) 20		
	Mean %	Range	%CV	Mean %	Range	%CV
5	14.3		22.82	23.4		14.62
10	83.3		2.40	87.2		4.74
15	98.3		1.97	100.0		4.04
20	100.3		2.29	102.3		2.49
30	100.6		2.29	102.0		2.30

The firm's response to comment #1 is acceptable.

Deficiency Comment #2

The firm should submit information on the lot/batch size of the test product, as well as the assay potency and content uniformity data for the test product.

The firm's response to comment #2

Lot size of the test product: apsules
Potency: 104.3%
Content uniformity: 102.7%

The firm's response to comment #2 is acceptable.

REVIEWER'S COMMENTS:

1. Under fasting conditions: The firm's in vivo bioequivalence study under fasting conditions demonstrated that the test product, Genpharm's Nicardipine HCl Capsules 30 mg and the reference product, Syntex's Cardene® Capsules 30 mg are bioequivalent. The 90% confidence intervals for the log-

transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were all within the acceptable range of 80-125%.

2. Under non-fasting conditions: The in vivo bioequivalence study under non-fasting conditions demonstrated that the test product, Genpharm's Nicardipine HCl Capsules 30 mg is bioequivalent to the reference product, Syntex's Cardene® Capsules 30 mg. The ratios of the test mean to the reference mean for the AUC_{0-t}, $AUC_{0-\infty}$, C_{max} were within the acceptable range of 0.8 to 1.25.

3. Dissolution Data: The firm has provided an acceptable comparative dissolution data for its drug product, Genpharm's Nicardipine HCl Capsules 30 mg and 20 mg, and the reference product, Syntex's Cardene® Capsules 30 mg and 20 mg. The firm conducted the dissolution test using FDA methodology.

RECOMMENDATIONS

1. The two in vivo bioequivalence studies (single-dose under fasting and single-dose non-fasting) conducted by Genpharm Inc. on its Nicardipine Hydrochloride 30 mg Capsule, bulk lot #101501 (package lot #101908), comparing it to the reference product Syntex's Cardene® 30 mg Capsule, lot #04860, have been found to be acceptable to the Division of Bioequivalence. The two studies demonstrate that under fasting and non-fasting conditions, Genpharm's Nicardipine Hydrochloride 30 mg Capsules are bioequivalent to Syntex's Cardene® 30 mg Capsules.

2. The dissolution testing data conducted by Genpharm Inc. on its drug product, Nicardipine Capsules, 30 mg strength (bulk lot #101501, package lot #101905) and 20 mg strength (bulk lot #101502, package lot #101910) have been found acceptable. The firm's formulation for the strength 20 mg is proportionally similar to the 30 mg strength capsule of the test product which underwent an acceptable bioequivalence study (ANDA #74-928, dated 01/31/1997). The waiver of the in vivo bioequivalence study requirements for the 20 mg strength of the test product is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems the 20 mg strength of the test product to be bioequivalent to the reference listed drug, Syntex's Cardene® Capsules 20 mg.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted using the following method: 900 ml 0.0333 M Citrate buffer pH 4.5 at 37°C applying USP 23 Apparatus II (Paddle) at 50 rpm, and

The test product should meet the following

specifications:

Not less than of the labeled amount of the drug product in the Capsule is dissolved in 30 minutes.

The firm should be informed of the recommendation.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE 7/14/97

Concur: _____ Date: 8/1/97
for Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA# 74-928, (original, duplicate), HFD-630, HFD-658 (Mhatre, Wahba), HFD-650 (Director), Drug File, Division File.
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