CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 075047

BIOEQUIVALENCE REVIEW

Acebutolol Hydrochloride
400 mg and 200 mg Capsules
ANDA # 75-047
Reviewer: Man M. Kochhar
75047SWD.197

Alphapharm Pty. Ltd.
Glebe NSW, Australia
Submission Date:
January 2, 1997

REVIEW OF BIOEQUIVALENCE STUDY, WAIVER REQUEST, AND DISSOLUTION DATA

(Fasting and Non-Fasting)

The purpose of this study is to compare the single-dose bioavailability of Alphapharm and Wyeth-Ayerst (Sectral) 400 mg acebutolol hydrochloride capsules under fasting and nonfasting conditions. In addition, the bioavailability of the Alphapharm product will be compared under nonfasting and fasting conditions. The firm has requested a waiver for their 200 mg capsules based upon 21 CFR 320.22.

BACKGROUND:

Acebutolol HCl is a selective, hydrophilic beta-adrenoreceptor blocking agent with mild intrinsic sympathomimetic activity. It is used in the management of hypertension and ventricular arrhythmias. The usual initial daily dose is 400 mg, which may be given once daily or divided into 2 doses.

Acebutolol HCL is well absorbed after oral administration, and is subject to an extensive first-pass effect, so that absolute bioavailability of the parent drug is approximately 40%. Protein binding in plasma is about 20%. The major metabolite is an N-acetyl derivative, diacetolol, and has pharmacological activity equal to that of acebutolol HCL. Within the single oral dose range of 200 to 400 mg, the kinetics of acebutolol and diacetolol are dose proportional. The half life of acebutolol is about 3 to 4 hours and of its metabolite diacetolol is 8 to 13 hours. Approximately 20 to 40% of an oral dose of acebutolol HCL is excreted in urine in the 24 hours after dosing: about 9 to 12% is excreted as unchanged drug, and 12 to 24% as diacetolol.

In-Vivo Study:

The objective was to determine if acebutolol HCL 400 mg capsules (test product) are bioequivalent to the reference product Sectral 400 mg capsules (Wyeth-Ayerst) under fasting and non-fasting conditions. The firm has requested for a waiver for their 200 mg capsules of acebutolol.

The study was conducted by Phoenix International Life Sciences Inc., Montreal, Canada, protocol # 920209, under the supervision

of Henri Navert, M.D. and Richard Lalonde, Pharm.D.

STUDY DESIGN:

Study # 1. The study was designed as open-label, randomized, 2-way crossover, single dose (400 mg capsule) study in 26 healthy volunteers under fasting conditions (Protocol # 960100).

Study # 2. The study was designed as a randomized, three-way crossover, single dose (400 mg capsule) study in 18 healthy volunteers under fasting and non-fasting conditions.

Subjects:

The study employed 26 healthy male volunteers (fasting) and 18 volunteers (non-fasting) between 18 and 45 years of age whose weight did not deviate by more than ±15% of the ideal for their height and age (Metropolitan Life Insurance Company Statistical Bulletin, 1983). Volunteers without history of asthma, nasal polyps, or serious cardiovascular, hepatic, renal, hematopoietic, peptic ulcer or gastrointestinal disease, alcohol or drug abuse were employed.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, and urinalysis). Subjects were not allowed to take any medication for 7 days prior to the study and to refrain from consumption of alcoholic or caffeine containing foods and beverages from 24 hours prior to dosing until study completion.

Sitting blood pressure and heart rate were measured before drug administration and at approximately 1, 2, 3, 4, 5, 6, and 24 hours post-dose. Vital signs were measured at other times when it was deemed necessary.

The subjects were housed in the Phoenix live-in facility from 12 hours before until 36 hours after the drug administration. Subjects will return for the blood draw at 48-hours.

Methods:

STUDY # 1

Fasting

The products and dosage employed in Study # 1 were as follows:

Treatment A. Test: One 400 mg capsule Acebutolol HCL (test drug, Alphapharm) lot # PA 137 with 240 ml of water.
Batch Size: (b)(4) Exp. Date: 1/98

Potency: 100.1% Content Uniformity: 98.2%

Treatment B: Reference: One 400 mg capsule of Sectoral (Wyeth-Ayerst), lot # 9950892, Exp. Date: 7/98

STUDY # 2

Non-Fasting

The product employed in this study were:

Treatment C. Test: One 400 mg capsule (test drug), acebutolol HCL, lot # PA137 with 240 mL of water (fasting).
Batch Size: [redacted] (b)(4) Expiry Date: 1/98
Potency: 100.1% Content Uniformity: 98.2%

Treatment D. Test: One 400 mg capsule (test drug), acebutolol Hcl, lot # PA 137 with 240 mL of water (non-fasting).

Treatment E. Reference: One 400 mg Sectral capsule (Wyeth-Ayerst), lot # 9950892 with 240 mL of water (non-fasting). Exp. Date: 7/98
Content Uniformity: 98.9%
Potency: 98.4%

In Study # 1 the subjects fasted for 10 hours prior to and 4 hours after the drug administration. Water ad lib was allowed except within 1 hour of drug administration.

In Study # 2 the subjects fasted for 10 hours prior to drug administration. The drug was administered 30 minutes after standard breakfast. Subjects were instructed to eat their entire meal in the time allotted. The first subsequent meal was served 4 hours after dosing.

In the fasting study (Treatment C), the subject fasted for 10 hours before dosing and for 4 hours thereafter (as in study # 1).

Ten (10) ml of venous blood were drawn in Vacutainers with EDTA at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 16, 24, 36, and 48 hours. The plasma was separated and promptly frozen for analysis.

WASHOUT PERIOD: 14 days

ANALYTICAL METHODOLOGY:

Plasma acebutolol and diacetolol were measured by a specific HPLC method using UV detection.

ASSAY VALIDATION:

FOR ACEBUTOLOL & DIACETOLOL (an active metabolite)

1. Linearity: 20 to 2000 ng/ml

2. Sensitivity: 20 ng/ml. Any sample below this concentration was reported as zero.

3. Specificity: Blank plasma sample from the subjects in the study indicated no interference with acebutolol or diacetolol or the internal standard.

4. Accuracy & Precision

Acebutolol

Between-Batch (N=8)

Actual (ng/ml)	20.00	60.00	750.00	1500.00
Observed (ng/ml)	19.84	53.01	772.21	1508.79
Accuracy %	99.20	88.40	103.00	100.60
CV %	6.9	6.5	1.5	5.9

Within-Batch (N=10)

Actual (ng/ml)	20.00	60.00	750.00	1500.00
Observed (ng/ml)	19.37	52.73	771.36	1574.98
Accuracy %	96.9	87.9	102.8	105.0
CV%	10.0	7.9	1.6	2.6

Diacetolol

Between-Batch (N=8)

Actual (ng/ml)	20.00	60.00	750.00	1500.00
Observed (ng/ml)	20.79	53.08	740.46	1499.83
Accuracy %	103.95	88.47	98.73	99.99
CV %	6.9	1.6	0.7	2.4

Within-Batch (N=10)

Actual (ng/ml)	20.00	60.00	750.00	1500.00
Observed (ng/ml)	21.36	54.18	744.28	1521.30
Accuracy %	106.8	90.3	99.2	101.4
CV%	4.8	3.8	1.0	1.3

5. The acebutolol and diacetolol assay procedures were validated by analyzing, in duplicate, plasma calibration standards spiked at four different acebutolol and diacetolol concentrations respectively on three separate occasions. Three separate

validation runs were performed on the same day.

6. The recovery was calculated on the basis of individual peak heights of extracted acebutolol and diacetolol against the mean of the peak heights obtained from neat acebutolol and diacetolol standards of the same concentrations.

7. Extraction recovery was determined by comparing peak areas of extracted calibration standards against those of unextracted calibration standards at three different concentrations. Results indicate that average recovery (n=6) of acebutolol was 93.13% at 60.0 ng/ml (CV 8.7%), 107.3% at 750.0 ng/ml (CV% 5.5%) and 107.17% at 1500.0 ng/ml (CV% 2.4%) and for diacetolol was 87.08% at 60 ng/ml (CV 6.3%), 94.60% at 750.0 ng/ml (CV 2.1%) and 96.30% at 1500.0 ng/ml (CV 2.4%).

8. Long term stability evaluation involves an analysis of replicates of stored samples at the approximate concentrations of low and high quality controls, together with samples from a similar number of replicates from the same batches (comparison samples), but stored in a liquid nitrogen container (approximately -160^{0}C). The evaluation uses chromatographic responses; i.e peak height or area ratio to the internal standard. It was stable at a nominal temperature of -20° C for 91 days. It was stable at a temperature of 22° C for 6 hours.

9.The freeze/thaw stability evaluation involves an analysis of replicates of stability samples which have been frozen and thawed three times, with freshly thawed (once only) comparison samples, each at approximately the concentrations of high and low QCs. The evaluation uses chromatographic responses i.e. peak height or area ratio to the internal standard or peak height or area where the analytical method does not involve an internal standard. Acebutolol HCL and Diacetolol were stable at the end of third freeze-thaw cycle.

DATA ANALYSIS:

Individual analysis of variance (ANOVA with factors including drug, phase, and sequence) were carried out to compare formulations at each sampling time, AUC (0-t), AUC (0-inf.), Cmax, Tmax, t1/2 and Kel. All ANOVAs were performed with SAS General Linear Models Procedures (GLM).

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

STUDY # 1 (FASTING)

TREATMENT A and B

Of the 26 subjects enrolled in the study, 5 did not complete the crossover. Subject # 3, 5, 9, 18, and 25 elected to withdraw from

the study for personal reasons. Thus a total of 21 subjects completed the crossover. The study was completed with no major protocol violations. The samples from all 21 subjects completing the study were assayed. The results of the study comparing the the bioavailability of acebutolol HCL capsules under fasting conditions are given in Table 1, 2, 3, 4, 5, and 6. The mean plasma acebutolol and diacetolol concentrations are given in Figure 1, and 2.

TABLE 1

Mean Plasma Concentration of Acebutolol (N=21)

Time (hours)	Alphapharm's Acebutolol, lot# PA137 ng/ml (CV%)	Wyeth-Ayerst's Sectoral, lot# 9950892 ng/ml (CV%)	T/R
0	0.00 (---)	0.00 (---)	0.00
0.5	343.47 (72)	310.66 (64)	1.10
1	466.68 (76)	455.21 (88)	1.02
1.5	713.21 (60)	602.85 (70)	1.18
2	720.13 (40)	711.89 (45)	1.01
2.5	671.27 (25)	740.24 (30)	0.91
3	641.23 (27)	657.59 (14)	0.97
3.5	555.78 (32)	575.42 (28)	0.96
4	477.21 (26)	504.33 (31)	0.95
6	279.18 (27)	293.43 (23)	0.95
8	163.80 (23)	178.50 (25)	0.92
12	71.24 (21)	74.24 (25)	0.96
16	36.04 (25)	37.26 (25)	0.97
24	5.44 (184)	6.10 (180)	0.89
36	0.00 (---)	0.00 (---)	0.00
48	0.00 (---)	0.00 (---)	0.00

TABLE 2

Mean Plasma Concentration of Diacetolol (N=21)

Time (Hours)	Alphapharm's Acebutolol, lot# PA137 ng/ml (CV%)	Wyeth-Ayerst's Sectoral, lot# 9950892 ng/ml (CV%)	T/R
0	0.00 (---)	0.00 (---)	0.00
0.5	114.80 (100)	78.72 (100)	1.46
1	325.01 (50)	329.98 (62)	0.98
1.5	508.59 (50)	433.99 (54)	1.17
2	707.00 (47)	644.33 (53)	1.09
2.5	809.04 (37)	775.02 (41)	1.04
3	871.94 (34)	860.56 (34)	1.01
3.5	865.58 (27)	895.96 (33)	0.97
4	847.71 (24)	865.25 (29)	0.98
6	669.97 (23)	688.94 (23)	0.97
8	541.06 (21)	545.29 (23)	0.99
12	351.22 (27)	365.63 (30)	0.96
16	268.93 (21)	269.73 (31)	0.99
24	169.10 (28)	164.94 (34)	1.02
36	74.84 (29)	78.37 (45)	0.95
48	53.85 (52)	61.27 (39)	0.88

TABLE 3

A Summary of Pharmacokinetic Parameters for Acebutolol (N=21)

Parameters	Alphapharm's Mean (CV%)	Wyeth-Ayerst's Mean (CV%)	T/R
AUC_{0-48} ng.hr/ml	4126.8 (19)	4219.4 (20)	0.98
AUC_{inf} ng.hr/ml	4282.1 (19)	4379.4 (19)	0.98
C_{max} ng/ml	987.2 (29)	1002.9 (32)	0.98
T_{max} hours	1.98 (41)	2.43 (31)	0.81

K_{el} 1/hr	0.1981 (16)	0.2000 (16)	0.99
$t_{1/2}$ hour	3.60 (19)	3.57 (18)	1.01
			90% Confidence Interval
Ln AUC_{0-48} ng.hr/ml	4053.5 (20)	4135.9 (21)	93; 103
Ln AUC_{inf} ng.hr/ml	4209.1 (19)	4299.0 (20)	93; 103
Ln C_{max} ng/ml	948.5 (30)	960.0 (31)	88; 109

TABLE 4

A Summary of pharmacokinetic Parameters for Diacetolol (N=21)

Parameters	Alphapharm's Mean (CV%)	Wyeth-Ayerst's Mean (CV%)	T/R
AUC_{0-48} ng.hr/ml	12027.2 (24)	12142.6 (28)	0.99
AUC_{inf} ng.hr/ml	13111.0 (24)	13295.1 (29)	0.99
C_{max} ng/ml	973.5 (28)	964.8 (33)	1.01
T_{max} hours	3.17 (30)	3.26 (18)	0.97
K_{el} 1/hr	0.0567 (16)	0.0557 (13)	1.01
$t_{1/2}$ hours	12.5 (13)	12.6 (13)	0.99

			90% Confidence Interval
Ln AUC_{0-48} ng.hr/ml	11713.7 (24)	11712.4 (28)	95; 105
Ln AUC_{inf} ng.hr/ml	12749.8 (24)	12798.8 (28)	94; 105
Ln Cmax ng/ml	937.2 (29)	916.8 (33)	95; 111

TABLE 5

A Summary of Ratios of Cmax, AUCo-t and AUCinf for Individual Pharmacokinetic Parameters for Acebutolol

Subject	T/R Cmax	T/R AUCo-t	T/R AUCinf
1	1.22	1.25	1.22
2	1.33	0.97	0.98
4	0.86	0.86	0.85
6	1.67	1.24	1.23
7	0.48	0.91	0.91
8	0.93	1.09	1.09
10	0.73	1.27	1.26
11	0.95	0.96	0.95
12	1.74	1.07	1.04
13	0.76	0.89	0.90
14	0.96	0.78	0.78
15	0.96	0.92	0.92
16	0.97	0.83	0.85
17	0.82	0.91	0.91
19	1.09	0.97	0.96
20	0.99	0.93	0.93
21	0.73	0.89	0.90
22	1.16	1.08	1.08
23	0.95	0.94	0.95
24	1.09	0.91	0.91
26	1.14	1.11	1.10
Mean	**1.02**	**0.99**	**0.98**
CV%	**29**	**19**	**19**

TABLE 6

A Summary of Ratios of Cmax, AUCo-t, AUCinf for Individual Pharmacokinetic parameters for Diacetolol

Subjects	T/R Cmax	T/R AUCo-t	T/R AUCinf
1	1.23	1.22	1.14
2	0.89	0.84	0.81
4	1.03	0.95	0.97
6	1.30	1.17	1.20
7	1.06	0.93	0.94
8	1.26	1.18	1.18
10	0.82	1.04	1.07
11	0.98	1.01	1.00
12	0.94	0.96	0.96
13	0.81	0.83	0.79
14	0.86	0.81	0.83
15	1.00	1.02	1.04
16	0.79	0.93	0.97
17	1.14	0.99	1.00
19	1.57	1.14	1.15
20	1.30	1.01	0.98
21	0.72	0.80	0.79
22	1.12	1.02	1.01
23	0.87	0.98	1.04
24	0.98	1.02	0.99
26	1.20	1.26	1.20
Mean	**1.04**	**1.00**	**1.00**
CV%	**28**	**24**	**24**

The ratios of arithmetic means for acebutolol (with 90% confidence intervals) for AUC_{o-t}, AUC_{inf} and C_{max} were 0.98 (93-103, 0.98 (93-102), 0.98 (87-108, respectively. The ratios for Kel and t1/2 were 0.99 and 1.01, respectively. The T_{max} was 1.98 hours for the test product and 2.43 hours for the reference product. The firm did calculate Ln AUC and Ln C_{max} for acebutolol and the 90% confidence intervals for log-transformed parameters were 93 to 103 for Ln AUC_{o-t}, 93 to 103 for Ln AUC_{inf} and 88 to 109 for Ln C_{max}.

The acebutolol concentration/time profiles of the two products were same with less than 20% difference between the products being observed at each of the timed collection points.

The ratios of arithmetic means for diacetolol (with 90% confidence intervals) for AUC_{o-t}, AUC_{inf} and C_{max} were 0.99 (94-104), 0.99 (93-104) and 1.01 (93-110), respectively. The ratio for K_{el} was 1.01 and for $t_{1/2}$ was 0.99. The T_{max} was 3.17 hours for

the test product and 3.26 for reference product. The firm did calculate Ln AUC and Ln C_{max} for diacetolol and the 90% confidence intervals for log-transformed parameters were 95 to 105 for Ln AUC_{o-t}, 94 to 105 for Ln AUC_{inf} and 95 to 111 for Ln C_{max}.

The diacetolol concentration/time profiles of the two products were same with less than 20% difference between the products being observed at each of the timed collection points except at 0.5 hour.

Adverse Effects:

There were no serious adverse effects which required dropping any subject from the study or required therapeutic medical intervention.

On the basis of fasting in vivo bioavailability data it is determined that Alphapharm's acebutolol capsules 400 mg and Wyeth-Ayerst's Sectoral capsules, 400 mg are bioequivalent.

Study # 2

Non-Fasting

Of the 18 subjects enrolled in the study, one did not complete the crossover. Subject # 2 did not return for period three dosing for personal reasons. Statistical and pharmacokinetic analyses were performed using data from subjects who completed at least two periods of the study. Therefore, data from 18 subjects were analyzed. The results of the study comparing the bioavailability of acebutolol HCL capsules under non-fasting conditions are given in Tables 7, and 8 and figure 3 and 4.

TABLE 7

MEAN PLASMA CONCENTRATIONS OF ACEBUTOLOL (N=18)

Time (hours)	Alphapharm's ACEBUTOLOL Lot # PA137 ng/ml (CV%) Treat. C	Alphapharm's ACEBUTOLOL Lot # PA137 ng/ml (CV%) Treat. D	WYETH's SECTORAL Lot # 9950892 ng/ml (CV%) Treat. E	T/R D/E
	FASTING	NONFASTING	NONFASTING	
0	0.00	0.00	0.0	0.00
0.5	330.4 (236)	101.3 (209)	94.0 (243)	1.08
1	564.0 (52)	256.1 (126)	257.3 (181)	0.99
1.5	698.7 (48)	491.8 (91)	386.3 (97)	1.27
2	756.2 (52)	614.3 (52)	543.5 (66)	1.13
2.5	747.0 (33)	693.1 (36)	611.8 (38)	1.13
3	705.2 (30)	669.0 (31)	640.1 (31)	1.04
3.5	624.7 (28)	641.5 (31)	595.1 (36)	1.08
4	526.0 (28)	561.9 (29)	550.7 (35)	1.02
5	405.2 (27)	546.9 (29)	537.1 (28)	1.02
6	307.3 (24)	419.6 (28)	435.2 (29)	0.96
8	178.9 (26)	247.9 (26)	252.7 (29)	0.98
12	74 9 (24)	105.0 (23)	107.5 (29)	0.98
16	34.2 (38)	52.8 (27)	56.8 (40)	0.93
24	4.5 (223)	19.5 (79)	18.7 (103)	1.04
36	0.0	2.6 (291)	4.2 (234)	0.62
48	0.0	0.0	0.0	0.00
DIACETOLOL				
0	0.0	0.0	0.0	0.00
0.5	80.6 (103)	33.5 (257)	39.7 (301)	0.84
1	337.7 (39)	92.2 (158)	99.8 (236)	0.92
1.5	533.0 (39)	231.1 (110)	220.4 (154)	1.04
2	648.5 (40)	345.7 (72)	302.5 (86)	1.14
2.5	763.4 (30)	458.0 (41)	404.7 (52)	1.13
3	831.4 (26)	513.6 (30)	506.0 (36)	1.01
3.5	890.4 (29)	551.1 (27)	543.7 (31)	1.01
4	856.3 (29)	564.5 (26)	564.1 (28)	1.00
5	816.3 (28)	610.9 (22)	612.4 (22)	0.99
6	693.7 (25)	573.7 (25)	574.5 (19)	0.99
8	515.9 (24)	460.4 (17)	466.5 (16)	0.98
12	357.3 (23)	305.5 (16)	312.5 (21)	0.98
16	237.2 (23)	221.0 (20)	213.6 (19)	1.03
24	142.0 (29)	137.3 (17)	141.7 (19)	0.97
36	75.6 (36)	77.8 (29)	76.5 (30)	1.01
48	64.4 (59)	48.3 (39)	48.6 (48)	1.00

TABLE 8

A SUMMARY OF PHARMACOKINETIC PARAMETERS FOR ACEBUTOLOL (N=18)

Parameters	Alphapharm's Acebutolol (CV%)		Wyeth's Sectoral (CV%)	T/T	T/R
	Fasting C	Nonfasting D	Nonfasting E	C/D	D/E
AUC_{0-t} ng.hr/ml	4426.0 (23)	4881.2 (22)	4778.7 (20)	0.91	1.02
AUC_{0-inf} ng.hr/ml	4582.7 (22)	5071.2 (21)	4982.2 (20)	0.90	1.02
C_{max} ng/ml	980.5 (28)	869.9 (35)	893.4 (40)	1.13	0.97
T_{max} hours	2.0 (39)	2.9 (44)	3.4 (48)	0.69	0.85
$t_{1/2}$ hours	3.34 (21)	4.53 (44)	4.67 (49)	0.74	0.97
K_{el} 1/hr	0.2149 (17)	0.1720 (29)	0.1727 (33)	1.25	0.99
				Ratio of Least Square Means	
Ln AUC_{0-t} ng.hr/ml	4308.3 (25)	4755.9 (25)	4684.9 (21)		101.3%
Ln AUC_{inf} ng.hr/ml	4468.7 (24)	4950.3 (24)	4887.3 (21)		101.1%
Ln C_{max} ng/ml	937.8 (33)	824.4 (34)	839.8 (36)		99.9%
DIACETOLOL					
AUC_{0-t} ng.hr/ml	11640.8 (22)	9515.5 (14)	9490.2 (14)	1.22	1.00
AUC_{inf}	12727.8 (24)	10559.4 (13)	10537.0 (15)	1.20	1.00

ng.hr/ml								
C_{max} ng/ml	941.6	(26)	691.6	(21)	715.1	(28)	1.36	0.96
T_{max} hours	3.4	(21)	4.2	(35)	4.4	(34)	0.81	0.95
$t_{1/2}$ hours	12.9	(20)	13.5	(20)	13.4	(18)	0.95	1.00
K_{el} 1/hr	0.0555	(20)	0.0529	(18)	0.0538	(24)	1.05	0.98
							Ratio of Least Square Means	
Ln AUC_{0-t} ng.hr/ml	11391.1	(21)	9420.8	(15)	9396.2	(15)		97.9%
Ln AUC_{inf} ng.hr/ml	12423.0	(23)	10467.9	(14)	10406.8	(17)		98.4%
Ln C_{max} ng/ml	914.4	(25)	677.1	(22)	690.3	(28)		96.3%

The acebutolol AUC_{0-t} and AUC_{0-inf} produced by Alphapharm's formulation are 2.1% higher than the reference drug. The C_{max} is 2.6% lower than the reference. The T_{max} is 14.7% lower than the corresponding reference value. The K_{el} and $t_{1/2}$ values differ by 0.4% and 3.0%, respectively.

Diacetolol AUC0-t, AUCinf and Cmax produced by Alphapharm's formulation were 0.3% higher, 0.2% higher and 3.3% lower respectively than the values for the reference drug. Tmax was 4.5% lower for the test drug. t1/2 and Kel values differ only by less than 1.6%

ANOVA performed on the plasma acebutolol and diacetolol concentration data at each of the seventeen sampling times detected no statistically significant differences between the two formulations. The firm did calculate Ln AUC and Ln Cmax for acebutolol and diacetolol.

Nonfasting-fasting Comparison (Regimen D vs C) Alphapharm

ACEBUTOLOL

Results for untransformed parameter showed increase of 9.3% for

AUC and decrease of 12.7% for Cmax after the administration of food. Mean Tmax was practically same for fasting and non-fasting conditions.

DIACETOLOL

Results for untransformed parameters showed decreases of 22% for AUC and 36% for Cmax after the administration of food. Mean Tmax after fasting conditions was 3.4 hours and 4.2 hours after food administration.

Nonfasting Comparison (Regimen D vs E) Alphapharm vs Wyeth

ACEBUTOLOL

The ratios (C/D) for the untransformed parameters AUC0-t, AUCinf and Cmax were 1.02, 1.01, 0.97 respectively. Mean Tmax values were 2.97 and 3.39 hours for Alphapharm (D) and Wyeth (E) products, respectively.

The ratios for least-square means for AUCo-t, AUCinf and Cmax were 101.3%, 101.1% and 99.9% respectively.

DIACETOLOL

The ratios (C/D) for the untransformed parameters AUC0-t, AUCinf, and Cmax were 1.0, 1.0 and 0.97 respectively. Mean Tmax were 4.1 and 4.4 hours for Alphapharm (D) and Wyeth (E) products, respectively.

The ratios for least-square means for AUCo-t, AUCinf and Cmax were 97.7%, 98.4% and 96.3% respectively.

No serious clinical events were reported by any of the other subjects.

The non-fasting in vivo bioavailability data demonstrates that Alphapharm's acebutolol capsules, 400 mg and Wyeth's Sectoral capsules 400 mg are bioequivalent.

DISSOLUTION TEST RESULTS:

In vitro dissolution testing was conducted in 900 ml of deaerated water at 37°C using USP XXIII apparatus 2 (Paddle) at 50 rpm. Results are presented in Table 9. Both the test and reference products meet the dissolution specifications of not less than 80% of the labeled amount of drug dissolved from the capsules in 30 minutes.
The batch size was (b) (4) capsuless.

The firm has demonstrated that the formulations of its acebutolol HCL capsules, 400 mg and 200 mg are proportionally similar with respect to active and inactive ingredients (Table 8).

COMMENTS:

FASTING:

1. Of the 26 subjects enrolled in the study, 21 completed the crossover. Subject # 3, 5, 9, 18, and 25 elected to withdraw from the study for personal reasons. The plasma samples from 21 subjects were assayed for acebutolol and diacetolol as per protocol. The plasma concentration of the test 400 mg acebutolol HCL capsule was compared to the plasma concentration from the reference Sectoral capsule, 400 mg. The acebutolol and diacetolol T/R ratios for AUCo-t, AUCinf and Cmax for 400 mg capsules were well within the range of 0.8 to 1.2.

2. Analysis of variance indicated no statistically significant treatment differences for AUC and Cmax for acebutolol and diacetolol. The 90% confidence intervals are within 80% to 125% for all the log transformed pharmacokinetic parameters for acebutolol and diacetolol.

3. The assay validation studies conducted by the sponsor are acceptable to the Division of Bioequivalence.

4. No serious adverse reactions were observed by any subject.

5. The dissolution testing conducted by the sponsor is acceptable to the Division of Bioequivalence.

6. The in vivo fasting bioequivalence study for 400 mg capsule of acebutolol HCL is acceptable.

NON-FASTING

1. Of the 18 subjects enrolled in the study, Subject # 2 did not return for Period 3 dosing for personal reason. As stated in the protocol, statistical and pharmacokinetic analyses were performed using data from subjects who completed at least 2 periods of the study. Therefore, data from 18 subjects were analyzed. The acebutolol ratios of Alphapharm formulation (fasting) to Alphapharm (non-fasting) for AUC0-t, AUCinf and Cmax were 0.91, 0.90 and 1.13 respectively. These ratios for diacetolol AUC0-t, AUCinf, and Cmax were 1.22, 1.20 and 1.36 respectively. Analysis of variance indicated no statistical significant treatment differences for AUC and Cmax for acebutolol or diacetolol. The geometric means were within limits set by the

Division of Bioequivalence. The Alphapharm and Wyeth acebutolol HCL capsules, 400 mg, show comparable bioavailability under nonfasting conditions.

3. The validation studies conducted by the sponsor are acceptable to the Division of Bioequivalence.

4. No serious adverse reactions were observed.

5. The in vivo non-fasting bioequivalence study and in vitro dissolution testing are acceptable.

GENERAL:

1. Sitting blood pressure and heart rate measurements were monitored at approximately 1, 2, 3, 4, 5, 6, and 24 hours after drug administration. Data from all subjects to complete the crossover were used in this analysis. Clinical vital signs were analyzed for statistical differences. There were virtually no statistical differences in the parameters tested; these included systolic and diastolic blood pressure and pulse rate.

2. The in vitro dissolution testing conducted for 200 mg and 400 mg capsules of the test and reference products shows greater than 80% of the labeled amount of the acebutolol HCL dissolved in 30 minutes.

3. The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

4. The firm has demonstrated that the formulation of its acebutolol HCL capsules 200 mg and 400 mg, are proportional with respect to active and inactive ingredients (Table 8).

DEFICIENCY: none

RECOMMENDATIONS:

1. The fasting and non-fasting bioequivalence studies conducted by Alphapharm Private Ltd. on its Acebutolol Hydrochloride Capsules, 400 mg lot # PA 137, comparing it to Sectoral Capsules, 400 mg, lot # 9950892, manufactured by Wyeth-Ayerst have been found acceptable by the Division of Bioequivalence. The studies demonstrate that under fasting and non-fasting conditions the Alphapharm's Acebutolol Capsules 400 mg are bioequivalent to the reference product, Sectoral 400 mg manufactured by Wyeth-Ayerst.

2. The in vitro dissolution testing conducted for 200 mg and 400 mg capsules for the test and reference products is acceptable. The formulation for 200 mg Acebutolol Hydrochloride Capsules is

proportionally similar to 400 mg Capsules which underwent fasting and non-fasting bioequivalent studies. The waiver of in vivo bioequivalence study requirement for Alphapharm's Acebutolol Hydrochloride 200 mg Capsule is granted. The 200 mg Acebutolol Hydrochloride Capsules from Alphapharm's are, therefore, deemed bioequivalent to 200 mg Sectoral Capsules manufactured by Wyeth Ayerst based on 21 CFR 320.22.

3. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 ml of deaerated water at 37°C using USP XXIII apparatus 2 (Paddles) at 50 rpm. The test should meet the following specifications:

> Not less than 80% of the labeled amount of the drug in the capsule is dissolved in 30 minutes.

4. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution testing and the study is acceptable.

The firm should be informed of the recommendations.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Ramakant M. Mhatre, Ph.D
Chief, Review Branch III
Division of Bioequivalence

10/6/97

Concur:

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

Date: 11/20/97

MMKochhar/mmk/6-24-947; 9-3-97; 9-19-97; 75-047 BIO

cc: ANDA # 75-047 original, HFD-630, HFD-600 (Hare), HFD-630 (Cviswanathan), HFD-650 (Fleischer), HFD-658 (Mhatre, Kochhar), Drug File, Division File.

Table 9 . In Vitro Dissolution Testing

Drug (Generic Name): Acebutolol
Dose Strength:400 mg
ANDA No.:75-047
Firm:Alphapharm
Submission Date: December 11, 1996
File Name:

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle:X RPM: 50
No. Units Tested: 12
Medium: Volume: 900 ml Deaerated Water
Specifications: NLT 80% in 30 minutes
Reference Drug: Sectoral
Assay Methodology: HPLC UV

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # PA 137 Strength(mg) 400			Reference Product Lot # 9950892 Strength(mg) 400		
	Mean %	Range	%CV	Mean %	Range	%CV
10	92	(b) (4)	6.8	90	(b) (4)	12.1
20	100		4.3	99		4.5
30	101		3.5	99		2.7

Sampling Times (Minutes)	Test Product Lot # PA138 Strength(mg) 200			Reference Product Lot # 9950621 Strength(mg) 200		
	Mean %	Range	%CV	Mean %	Range	%CV
10	96	(b) (4)	6.7	77	(b) (4)	14.2
20	101		2.6	96		7.3
30	102		1.9	98		2.9

TABLE 10

FORMULATION

Ingredients	400 mg Capsules mg per Capsule	200 mg Capsules mg per Capsule
Acebutolol HCL*	443.4	221.7
equivalent to Acebutolol	400.0	200.0
Povidone, USP	(b) (4)	
Maize Starch, NF		
Stearic Acid, NF		
(b) (4)		
TOTAL	508.0	254.0

* As Acebutolol (b) (4)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-047 APPLICANT: Alphapharm Pty. Ltd.

DRUG PRODUCT: Acebutolol Hydrochloride 200 mg, 400 mg

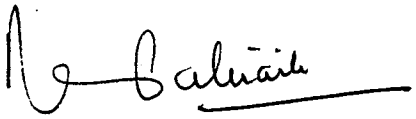
The Division of Bioequivalence has completed its review and has no further questions at this time.

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 deaerated water, at 37°C, using USP Apparatus 2 (Paddles) at 50 rpm. The test product should meet the following specifications:
>
> Not less than 80% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 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,



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

11/20/97

CC: ANDA 75-047
ANDA DUPLICATE
DIVISION FILE
HFD-650/Division Sign Off
HFD-650/M. Kochhar
BIO DRUG FILE
FIELD COPY

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BIOEQUIVALENCY - ACCEPTABLE

11 Dec 96

1. **FASTING STUDY** (STF) Strengths: 400 mg
Clinical: Phoenix International
Analytical: _____
Outcome: (AC) IC UN NC

2. **FOOD STUDY** (STP) Strengths: 400 mg
Clinical: Phoenix International
Analytical: _____
Outcome: (AC) IC UN NC

3. **MULTIPLE DOSE STUDY** (STM) Strengths: _____
Clinical: _____
Analytical: _____
Outcome: AC IC UN NC

4. **DISSOLUTION DATA** (DIS) All Strengths
Outcome: AC IC UN NC

5. **STUDY AMENDMENT** (STA) Strengths: _____
Outcome: AC IC UN NC

6. **WAIVER** (WAI) Strengths: _____
Outcome: AC IC UN NC

11 Dec 96 - 7. **DISSOLUTION WAIVER** (DIW) Strengths: 200 mg
Outcome: (AC) IC UN NC

8. **OTHER** (OTH) diskette
May 7, 97 submission Strengths: _____
Outcome: AC IC UN (NC)

9. **OTHER OPTIONS** (less common): Strengths: _____
a. Protocol (PRO)
b. Protocol Amendment (PRA)
c. Protocol/Dissolution (PRD)
d. Special Dosage (STS)
e. Study/Dissolution (STD)
f. Bio study (STU)
Outcome: AC IC UN NC

OUTCOME DECISIONS:
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete

WINBIO COMMENTS:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 75-047 SPONSOR: Alphapharm
DRUG: Acebutolol HCl
DOSAGE FORM: Capsules
STRENGTH(s): 400 mg and 200 mg
TYPE OF STUDY: Single/~~Multiple~~ Fasting/Fed
STUDY SITE: Phoenix

STUDY SUMMARY: The bioequivalence studies conducted on Acebutolol HCl 400 mg capsules are acceptable

DISSOLUTION: Dissolution testing is acceptable Waiver is granted for the 200 mg strength

PRIMARY REVIEWER: BRANCH:

INITIAL: DATE:

BRANCH CHIEF: Mahesh N. Makary BRANCH: HT

INITIAL: MNM DATE: 2/17/98

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: DPE DATE: 2/19/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE: