CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-364/SE8-016

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:20,364 (SE8-016) **Submission Date:** June 29, 2001

Drug Name:	Lotrel (amlodipine 10 mg and benazepril hydrochloride 20 mg)
Formulation:	Capsules, 10/20 mg
Applicant:	Novartis Pharmaceuticals Co
Submission:	Supplemental NDA: Change to approved product (new strength)
Reviewer:	Elena V. Mishina, Ph.D.

BACKGROUND:

Lotrel (amlodipine and benazepril hydrochloride combination capsules) is approved by the Agency with the NDA 20,364 for the initial therapy of hypertension. Amlodipine is a dihydropyridine calcium channel blocker that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and a subsequent reduction in blood pressure. The active metabolite of benazepril, benazeprilat is a nonsulfhydryl, selective ACE inhibitor that lowers blood pressure primarily through its action on the renin-angiotensin-aldosterone system. The marketed combination capsules of Lotrel are formulated with 2.5/10 mg, 5/10 mg, and 5/20 mg fixed combination of amlodipine besylate and benazepril hydrochloride. The sponsor is proposing to market a new, higher dosage strength capsule, which contains 10 mg of amlodipine and 20 mg of benazepril. One clinical study (protocol 104) supported the efficacy and safety claim for a new dosage strength. This clinical study was a double-blind, randomized, placebo-controlled, forced-titration, parallel-group trial in patients with essential hypertension. Patients were randomized to receive either Lotrel 5/10 mg or placebo for 2 weeks. Those patients receiving Lotrel were titrated to either Lotrel 5/20 or Lotrel 10/20 mg (i.e. two 5/10 capsules) for 6 weeks. The purpose of this trial was to evaluate the safety and efficacy of Lotrel in total daily doses of 10/20 mg vs 5/20 mg, and vs placebo in patients with essential hypertension.

The ingredients are identical in the marketed and the new to-be-marketed Lotrel formulation. The new product will be identical to the 5/20 mg Lotrel formulation with the only difference in formulation being that the _____.

The sponsor submitted for review a study, which was designed to assess the bioequivalence between the two 5/10 mg amlodipine/benazepril capsule (used in protocol 104) and one 10/20 mg amlodipine/benazepril, the final market image (FMI) capsule.

Additionally, the sponsor compared in vitro the dissolution performance of 5/10 mg and 10/20 mg amlodipine/benazepril capsules in the prescribed media. With this supplemental NDA **20,364 (SE8-016)**, the sponsor submitted for review the results of this study.

RESULTS:

The clinical trial formulation (2x5/10 mg Lotrel capsules), test, and the final market image capsule (1x10/20 mg Lotrel capsule), reference, were bioequivalent based on the comparison of AUC for all components: amlodipine, benazepril and its active metabolite, benazeprilat. These formulations were equivalent based on the comparison of Cmax for amlodipine and benazeprilat (active metabolite) but not for the Cmax of the parent drug benazepril. After Lotrel dose administration, the plasma concentrations of the parent drug benazepril peaked at about 0.7 hours and was not detectable in plasma after 6 hours post-dose due to the hydrolysis into its metabolite, benazeprilat. Benazeprilat plasma concentrations peaked at 1.36 hours and were on average 1.5-3 times higher than that of the parent drug. Therefore, the failure to meet the 90% confidence interval for the Cmax values of the parent drug benazepril is not going to be of any significant clinical consequence since the parent drug has much smaller activity than the metabolite and benazepril is quickly converted to the metabolite. Only trace amounts of the parent drug are recovered in urine.

The main pharmacokinetic parameters are summarized in Table 1 and Table 2.

Table 1. Pharmacokinetic parameters for benazepril, benazeprilat, and amlodipine.

Summary statistics of pharmacokinetic parameters of benazepril, benazeprilat and amlodipine after treatment A (one 10/20 mg amlodipine/benazepril capsule and after treatment B (two 5/10 mg amlodipine/benazepril capsules).

Analyte		t_{max}* h	C_{max} ng/ml	$AUC_{0-\infty}$ ng*h/ml	AUC_{0-t} ng*h/ml	$t_{½}$ h	t_{max} h	C_{max} ng/ml	$AUC_{0-\infty}$ ng*h/ml	AUC_{0-t} ng*h/ml	$t_{½}$ h
Benaz-epril		treatment A (one 10/20 mg amlodipine/benazepril capsules)					treatment B (two 5/10 mg amlodipine/benazepril capsules)				
	Mean	0.70	439	410	404	0.70	0.79	343	387	379	1.2
	SD	0.25	222	180	180	0.15	0.25	169	153	151	3.0
Benaz-eprilat	Mean	1.36	654	3050	2978	13.3	1.44	659	3188	3118	12.6
	SD	0.34	144	717	708	9.8	0.30	200	818	813	7.7
	90% C.I. of ratios	$AUC_{0-\infty}$ (ng*h/ml) 0.92, 0.99 AUC_{0-t} (ng*h/ml) 0.92, 0.99 C_{max} (ng/ml) 0.92, 1.06									
Amlod-ipine	Mean	9.88	5.8	302	276	39.2	9.88	6.1	326	294	40.9
	SD	4.74	1.8	104	87	7.9	4.66	1.7	89	75	9.7
	90% C.I. of ratios	$AUC_{0-\infty}$ (ng*h/ml) 0.86, 0.97 AUC_{0-t} (ng*h/ml) 0.87, 0.98 C_{max} (ng/ml) 0.89, 1.02									

* The median value for t_{max} was 1.5 h for both treatments for benazeprilat and 8 h for both treatments for amlodipine (see attachment A and Study 2301 report)

Table 2. Summary statistics and confidence intervals for benazepril (parent drug).

Assessment of bioequivalence between 1X10/20mg and 2X5/10mg treatments for Benazepril

Parameters (unit)	Treatment	N	Arithmetic mean	Standard deviation	Percent difference	Geometric mean	Ratio of geometric means	90% CI for ratio
AUC(0-inf) (ng.h/mL)	1X10/20 mg	33	409.8	180.0	5.79	373.8	1.04	(0.98, 1.11)
	2X 5/10 mg	33	387.3	153.0		358.8		
AUC(0-t) (ng.h/mL)	1X10/20 mg	33	403.8	180.5	6.46	367.2	1.05	(0.98, 1.12)
	2X 5/10 mg	33	379.3	150.5		350.9		
Cmax (ng/mL)	1X10/20 mg	33	439.2	221.9	28.08	382.5	1.26	(1.12, 1.40)
	2X 5/10 mg	33	342.9	168.5		304.5		

Additionally, the in vitro comparative dissolution study showed that the two products have similar dissolution profiles in the approved medium for both benazepril and amlodipine.

RECOMMENDATION

The application is acceptable for meeting the recommendations of the Office of Clinical Pharmacology and Biopharmaceutics. The same dissolution specifications for the new capsule strength recommended as was adopted for the other strength.

CPB Briefing held on March 12, 2002. Attendees: Drs. M. Mehta, P. Marroum, J. Lazor.

/S/

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

/S/

Date

/S/

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

cc list: NDA 20364, MehulM, MishinaE, HFD 110 BIOPHARM

APPENDIX I

Study Report

A Randomized, Open-Label, Crossover Bioavailability Study Comparing 5/10 mg and 10/20 Amlodipine/Benazepril Fixed Combination Capsules

STUDY ID: CCIB002G 2301 **Volumes:** **6-8**

Principal Investigator:

Clinical Laboratories:

OBJECTIVES:

To assess the bioequivalence between two 5/10 mg amlodipine/benazepril capsules and one 10/20 mg amlodipine/benazepril the final market image capsule.

METHODS:

Study Design:

Open label, randomized, two-way, single dose, single center crossover trial in healthy male and non-fecund female volunteers with a two or three week washout period between doses. Subjects received two 5/10 mg amlodipine/benazepril during one period and one 10/20 mg amlodipine/benazepril, the final market image (FMI) capsule during the alternate period.
Healthy subjects were screened within at least 12 hours prior to the first dose period. Initially, 36 subjects were enrolled followed by additional 6 subjects as replacement subjects. Totally, 42 subjects were enrolled and 35 subjects completed the study. In Period I, all subjects were randomly assigned to Treatment A or B. In dosing Period II, subjects received an alternative treatment. The capsules were taken with 240 mL of water after 10 hours of overnight fast. Caffeine containing food had to be discontinued 48 hours before dosing. Subjects remained upright and fasting for the next 4 hours after dosing.

Formulations:

Treatment A, test product: one 10/20 mg amlodipine/benazepril capsule
Batch no:/Plant/ Date of manufacturing: 457150/ /June-1999/
Lot # 501066,

Treatment B, reference product: two 5/10 mg amlodipine/benazepril capsules
Batch no:/Plant/ Date of manufacturing: 564001T/ /September-2000

Lot # 501194,

Mode of administration. Single oral dose.

Washout period. Each period was separated by at least 7-day wash-out.

Biological Analytes: Blood samples were collected pre-dose and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 48, 72, and 144 hours post-dose.

Assay:

The plasma samples were assayed for benazepril and benazeprilat using a validated [redacted] method.

Specificity: chromatograms not shown.

Linearity: satisfactory. The assay calibration range was [redacted] ng/mL to [redacted] mcg/mL for benazepril and benazeprilat.

Limit of quantitation was set to [redacted] ng/mL .

Precision and accuracy were satisfactory (shown in Table 1).

The plasma samples were assayed for amlodipine using [redacted] method.

Specificity: chromatograms not shown.

Linearity: satisfactory. The assay calibration range was [redacted] ng/mL to [redacted] ng/mL for amlodipine.

Limit of quantitation was set to [redacted] ng/mL.

Precision and accuracy were satisfactory (shown in Table 2).

Intra-assay

Benazepril:

At the limit of quantitation:
CV [redacted] %
All other concentrations:
CV between [redacted] and [redacted] %

Benazeprilat:

At the limit of quantitation
CV [redacted] %
All other concentrations
CV between [redacted] and [redacted] %

Amlodipine:

At the limit of quantitation
CV [redacted] %
All other concentrations
CV between [redacted] and [redacted] %

Daily variation:

Benazepril: CV (R^2) [redacted]
Benazeprilat: CV (R^2) [redacted]
Amlodipine: CV (R^2) [redacted]

Inter-assay:
Benazepril: Accuracy ranged from 98.0 to 102%
Benazeprilat: Accuracy ranged from 98.1 to 102%.

Summary of accuracy and precision of QC samples for benazepril and benazeprilat is shown in Table 1.
Table 1.

Summary of accuracy and precision of QC samples for benazepril and benazeprilat

Nominal con. In QC samples (ng/mL)	Number of determinations	Mean accuracy (%)	Precision (%)
Benazepril			
7.50	70	94.3	
250	71	93.6	
900	72	94.7	
Benazeprilat			
7.50	67	103	
250	72	104	
900	72	104	

Summary of accuracy and precision of QC samples for amlodipine is shown in Table 2.
Table 2

Summary of accuracy and precision of QC samples for amlodipine

Nominal con. In QC samples (ng/mL)	Number of determinations	Mean accuracy (%)	Precision (%)
Amlodipine			
0.108	51	96.0	
3.60	51	96.6	
10.8	50	96.8	

Data Analysis: Pharmacokinetic parameters (AUCt and AUCinf) were calculated using noncompartmental methods. Cmax and Tmax values were extracted from raw data. ANOVA model (PROC MIXED SAS procedure) was used to compare the effect of treatment. The sources of variation included sequence, subject with sequence, period, treatment with subject (sequence) as random effect. ANOVA was performed on log-transformed parameters. Each of the pharmacokinetic parameters was statistically analyzed separately.
The main pharmacokinetic parameters are statistically compared in the Table 3 and Table 4.
Table 3.

Summary statistics of pharmacokinetic parameters of benazepril, benazeprilat and amlodipine after treatment A (one 10/20 mg amlodipine/benazepril capsule and after treatment B (two 5/10 mg amlodipine/benazepril capsules).

Analyte		t_{max} h	C_{max} ng/ml	$AUC_{0-\infty}$ ng*h/ml	AUC_{0-t} ng*h/ml	$t_{½}$ h	t_{max} h	C_{max} ng/ml	$AUC_{0-\infty}$ ng*h/ml	AUC_{0-t} ng*h/ml	$t_{½}$ h
Benaz-epril		treatment A (one 10/20 mg amlodipine/benazepril capsules)					treatment B (two 5/10 mg amlodipine/benazepril capsules)				
	Mean	0.70	439	410	404	0.70	0.79	343	387	379	1.2
	SD	0.25	222	180	180	0.15	0.25	169	153	151	3.0
Benaz-eprilat	Mean	1.36	654	3050	2978	13.3	1.44	659	3188	3118	12.6
	SD	0.34	144	717	708	9.8	0.30	200	818	813	7.7
	90% C.I. of ratios	$AUC_{0-\infty}$ (ng*h/ml) 0.92, 0.99 AUC_{0-t} (ng*h/ml) 0.92, 0.99 C_{max} (ng/ml) 0.92, 1.06									
Amlod-ipine	Mean	9.88	5.8	302	276	39.2	9.88	6.1	326	294	40.9
	SD	4.74	1.8	104	87	7.9	4.66	1.7	89	75	9.7
	90% C.I. of ratios	$AUC_{0-\infty}$ (ng*h/ml) 0.86, 0.97 AUC_{0-t} (ng*h/ml) 0.87, 0.98 C_{max} (ng/ml) 0.89, 1.02									

* The median value for t_{max} was 1.5 h for both treatments for benazeprilat and 8 h for both treatments for amlodipine (see attachment A and Study 2301 report)

Table 4.

Assessment of bioequivalence between 1X10/20mg and 2X5/10mg treatments for Benazepril

Parameters (unit)	Treatment	N	Arithmetic mean	Standard deviation	Percent difference	Geometric mean	Ratio of geometric means	90% CI for ratio
AUC(0-inf) (ng.h/mL)	1X10/20 mg	33	409.8	180.0	5.79	373.8	1.04	(0.98, 1.11)
	2X 5/10 mg	33	387.3	153.0		358.8		
AUC(0-t) (ng.h/mL)	1X10/20 mg	33	403.8	180.5	6.46	367.2	1.05	(0.98, 1.12)
	2X 5/10 mg	33	379.3	150.5		350.9		
Cmax (ng/mL)	1X10/20 mg	33	439.2	221.9	28.08	382.5	1.26	(1.12, 1.40)
	2X 5/10 mg	33	342.9	168.5		304.5		

RESULTS:

After both treatments, plasma concentrations of all components showed similar profiles (Figures 1 and 2). Benazepril plasma concentrations increased quickly and declined rapidly (t1/2 ~ 1 hour), being detectable about 4-6 hours post dose administration. Benazeprilat plasma concentrations reached peak at about 2 hours and was detectable for up to 48 hours post-dose (t1/2 ~ 13 hours). Amlodipine plasma concentrations peaked at 6-10 hours and were detectable for up to 144 hours post-dose.

Figure 1

Mean plasma concentration values of benazeprilat after treatment A (test: one 10/20-mg amlodipine/ benazepril capsule) and treatment B (reference: two 5/10-mg amlodipine/ benazepril capsules). The error-bars represent standard of deviation (SD). Inset : Benazeprilat plasma concentration-time profile up to 144 hours.

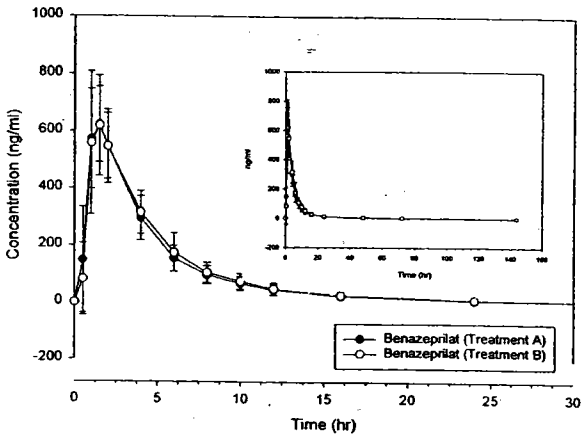
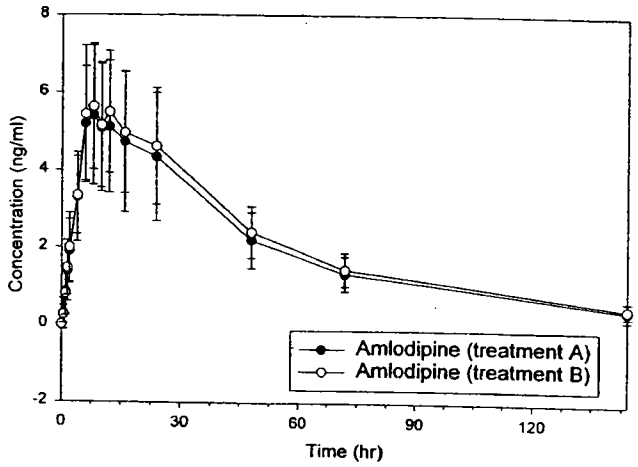


Figure 2

Mean plasma concentration values of amlodipine after treatment A (test: one 10/20-mg amlodipine/ benazepril capsule) and treatment B (reference: two 5/10-mg amlodipine/ benazepril capsules). The error-bars represent standard of deviation (SD)



Benazeprilat: no statistical sequence and treatment effects were observed. The calculated 90% confidence intervals were for the AUCinf ratio (0.92, 0.99), for the ration of AUCt (0.92, 0.99), and for the ratio of Cmax (0.95,1.06). Statistical results are shown in Table 5.

Table 5 Assessment of bioequivalence between 1X10/20mg and 2X5/10mg treatments for Benazeprilat

Parameters (unit)	Treatment mg	N	Geometic Means	Ratio of Geometric Means	90% C.I. for Ratio
$AUC_{(0-\infty)}$ (ng.h/mL)	1X10/20	33	2958.7	0.95	(0.92,0.99)
	2X 5/10	33	3100		
$AUC_{(0-t)}$ (ng.h/mL)	1X10/20	33	2886	0.95	(0.92,0.99)
	2X 5/10	33	3029.4		
C_{max} (ng/mL)	1X10/20	33	634.8	1.00	(0.95,1.06)
	2X 5/10	33	631.7		

Amlodipine: no statistical sequence and treatment effects were observed. The calculated 90% confidence intervals were for the ratio of AUCinf (0.86, 0.97), for the ratio of AUCt (0.87, 0.98), and for the ratio of Cmax (0.89, 1.02). Statistical results are shown in Table 6.

Table 6 Assessment of bioequivalence between 1X10/20mg and 2X5/10mg treatments for Amlodipine

Parameters (unit)	Treatment mg	N	Geometic Means	Ratio of Geometric Means	90% C.I. for Ratio
$AUC_{(0-\infty)}$ (ng.h/mL)	1X10/20	33	285.6	0.91	(0.86, 0.97)
	2X 5/10	33	313		
$AUC_{(0-t)}$ (ng.h/mL)	1X10/20	33	262.9	0.93	(0.87, 0.98)
	2X 5/10	33	284.1		
C_{max} (ng/mL)	1X10/20	33	5.6	0.95	(0.89, 1.02)
	2X 5/10	33	5.9		

Dissolution:

The dissolution method used USP apparatus 1 with 500 mL of 0.01 N HCL at 37.0 ± 0.5°C at a paddle speed of 100 ± 4 rpm (approved dissolution method).

Dissolution profiles of 5/10 and 10/20 mg Lotrel capsuls were similar, Table 7.

Table 7. Dissolution Results.

The components and composition of a new higher strength of Lotrel hard gelatin capsuls is shown in Table

Attachment E Drug Product Dissolution Testing

Date of test	Dosage form and strength	Lot no:	Dissolution apparatus	Media, temperature (°C)	Speed of rotation / flow (r.p.m.)	Collection time (min)	No. units tested, mean % dissolved, individual values, % cv	
							Amlodipine	Benazepril
Feb-2001	10/20 mg capsule	564001T	USP #1	0.01N HCl, 37 °C	100	30	12 capsules Mean= 99; % cv	12 capsules Mean= 96; % cv
Jul-1999	5/10 mg capsule	457150	USP #1	0.01N HCl, 37 °C	100	30	6 capsules Mean= 99; % cv	6 capsules Mean= 101; % cv

8.

Components and composition of the new higher strength of Lotrel 10/20 mg hard gelatin capsules

INGREDIENT	AMOUNT PER CAPSULE (MG)	FUNCTION	REFERENCE TO STANDARD
Amlodipine besylate	13.888*	Active ingredient	Novartis
Microcrystalline cellulose			NF
Calcium phosphate, dibasic			USP
Sodium starch glycolate			NF
Magnesium stearate			NF
Benazepril hydrochloride tablets, 20 mg**	80.000		
Target capsule fill weight			
Capsule shell (theoretical weight)			
Target total capsule weight	357.000		

* Equivalent to 10.0 mg amlodipine base

** Composition is described in following table

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Table 9. Dissolution method and specification.

Attachment F Proposed Dissolution Method and Specification

Dosage form:	Capsule
Strength(s):	10/20 mg
Apparatus type:	USP #1
Media:	0.01 N Hydrochloric acid
Volume (mL):	500 mL
Speed of rotation (r.p.m.):	100 ± 4
Media temperature	37.0 ± 0.5 °C
Sample times (min):	30
Brief description:	

Dissolution specification:

Benazepril Hydrochloride:

Minimum % of labeled amount of Benazepril HCl dissolved in 30 minutes (Q= [redacted]

individual 6 of 6:	[redacted] %
- or - average of 12:	%
individual 12 of 12:	%
- or -average of 24:	%
individual 22 of 24:	%
individual 24 of 24:	%

Amlodipine:

Minimum % of labeled amount of Amlodipine dissolved in 30 minutes (Q = [redacted]

individual 6 of 6:	%
- or -average of 12:	%
individual 12 of 12:	%
- or -average of 24:	%
individual 22 of 24:	%
individual 24 of 24:	%

COMMENTS:

1. The sponsor did not calculate the similarity factor (f_2) and did not present the results of dissolution test graphically.
2. The number of capsules tested for the reference formulation was 6 instead of 12.
3. No chromatograms for the selectivity test of the assay were included in the submission.
4. No information on recovery was included in the assay validation.

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/s/

Elena Mishina
3/12/02 04:52:53 PM
BIOPHARMACEUTICS

Patrick Marroum
3/12/02 05:24:51 PM
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