CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-364/SE8-016

Medical Review(s)

MEDICAL REVIEW OF SAFETY AND EFFICACY

NDA#20,364
Type of Document: Supplementary NDA: change to approved product (new strength)
Drug Name: Lotrel® (amlodipine/benazepril combination product)
Sponsor: Novartis
Date of application: June 29, 2001
Medical Reviewer: Maryann Gordon, M.D.

Introduction

This submission is in support of a higher dosage strength (10 mg amlodipine with 20 mg benazepril HCl) in a capsule for oral administration. Currently, the approved Lotrel doses are 2.5/10, 5/10, and 5/20. The approved daily dose for amlodipine monotherapy is up to 10 mg. The 2 new studies conducted in support of the higher strength include protocol 104, a safety and efficacy trial, and protocol 2301, a bioequivalence trial. This medical review evaluates the safety and efficacy of protocol 104. No deaths or serious safety events were reported for the bioequivalence study 2301; the one drop out for adverse events was a subject who complained of back pain 21 days after dosing.

An agreement was made with Dr. Lipicky that it was not necessary for the sponsor to pool the safety data from protocol 104 with the Lotrel NDA safety database.

Conclusions

Lotrel 10/20 mg was numerically but not statistically better than Lotrel 5/20 mg in lowering sitting diastolic blood pressure (placebo subtracted mean changes from baseline at endpoint were -10.3 mmHg and -9.4 mmHg, respectively). Both doses were statistically superior to placebo. The placebo subtracted mean changes from baseline at endpoint for mean sitting systolic blood pressure were -17.5 mmHg for the higher Lotrel dose and -15.8 mmHg for the lower dose. A meta analysis using data from previous studies plus study 104 showed a tendency for higher doses of 1:2 dose ratio (amlodipine:benzapril) to lower diastolic and systolic blood pressure more than lower doses.

Patients who were randomized to Lotrel 10/20 mg were somewhat more likely to drop out of treatment for safety reasons (10/127, 7.9%) compared to the lower dose (6/125, 4.8%) and placebo (7/132, 5.3%). The 1 reported death (MI) occurred in a patient on the higher Lotrel dose. Edema was more likely to be reported by patients randomized to the 10/20 mg dose compared to the 5/20 mg dose (placebo subtracted incidence rates were 6.1% and -0.5%, respectively). The placebo subtracted rate reported in the original for the amlodipine 10 mg monotherapy was 10.2%.

The reporting rate for dyspepsia was 4% in the high dose Lotrel, but patients randomized to the lower dose or placebo did not report this event. The reporting rate for dizziness was 6.4% by patients randomized to the higher dose compared to 2.4% for the lower dose and 3.8% for placebo.

Although the number of females in protocol 104 was relatively small, more women on the high dose of Lotrel reported edema, cough, dizziness and headache compared to males taking the same dose.

Overall, the higher dose Lotrel 10/20 mg did not contribute much to blood pressure lowering effect, and it slightly increased the reporting of edema, dyspepsia, and dizziness, with women appearing to be the most affected.

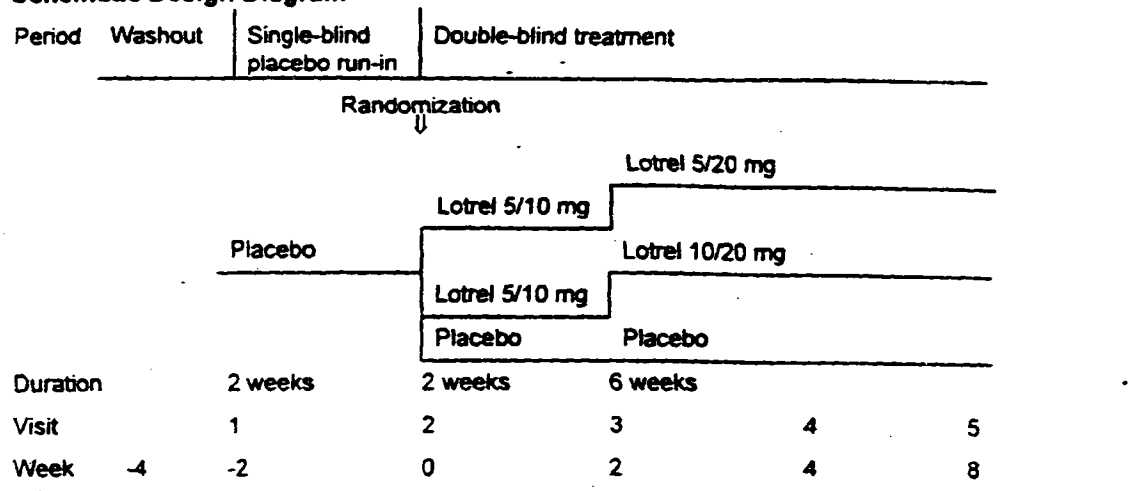
Protocol 104

1.0 Efficacy

1.1 Study Design: double blind, randomized, placebo controlled, forced titration, parallel group. The study consisted of a 2 week washout followed by a 2 week placebo run in. Patients were stratified based on race and randomization to either Lotrel (amlodipine/benazepril) 5/10 mg or placebo for 2 weeks followed by increasing dose of Lotrel to 5/20 mg or 10/20 mg (2 capsules 5/10mg) or remain on placebo for 6 weeks.

1.2 Study Objective: evaluate safety and efficacy (at trough) of Lotrel 10/20 mg qd compared to Lotrel 5/20 mg qd and placebo qd.

Schematic Design Diagram



1.3. Patient Type: patients with essential hypertension

1.3.1. Inclusion Criteria

-males or females (surgically sterile, menopausal for at least 1 year, or using acceptable for of birth control),
-between ages of 18-80 inclusive at time of screening
-have a diagnosis of uncomplicated essential hypertension. At visits 1 and 2, mean sitting diastolic blood pressure (MSDBP) must be $\geq$ 95 mmHg but $\leq$ 120 mmHg and difference between MSDBP at visits 1 and 2 must be $\leq$10 mmHg.

1.3.2 Exclusion Criteria

- Pregnancy, nursing mothers, or women of childbearing potential not practicing effective methods of contraception.
- Overt heart failure or a history of heart failure within the preceding 6 months.
- Second or third degree heart block.
- Concomitant angina pectoris.
- Clinically relevant arrhythmias. This is defined as any arrhythmia requiring medical therapy or that causes symptoms.
- Clinically significant valvular heart disease.
- Malignant hypertension.
- Evidence of a secondary form of hypertension, such as coarctation of the aorta, hyperaldosteronism, unilateral renal disease, or pheochromocytoma.
- Keith-Wagener Grade III or IV hypertensive retinopathy.
- Evidence of hepatic disease as determined by AST (SGOT) or ALT (SGPT) values two times the upper limit of normal.
- Evidence of renal impairment as determined by serum creatinine greater than 1.5 times the upper limit of normal.

- Diabetes mellitus with poor glucose control, peripheral neuropathy, or autonomic neuropathy.
- History of a myocardial infarction within the preceding 3 months.
- History of hypertensive encephalopathy, cerebrovascular accident, or transient ischemic attack within the preceding 6 months.
- History of allergies to ACE inhibitors and/or calcium entry blockers.
- History of severe, life threatening disease or any condition that in the opinion of the investigator or the sponsor would jeopardize the evaluation of efficacy or safety results.
- History of noncompliance to medical regimens and patients who are considered potentially unreliable.
- History of drug or alcohol abuse within the past 2 years.
- Other investigational drugs within the past 30 days.
- Unwillingness or inability to give informed consent

1.4 Sample Size: The total sample size needed was determined to be 300. The primary null hypothesis tested was that, with respect to change from baseline in mean sitting diastolic blood pressure (MSDBP), the treatment effect of Lotrel 5/10 —> 10/20 mg is equal to the treatment effect of Lotrel 5/10 —> 5/20 mg versus the alternative hypothesis that the treatment effect of Lotrel 5/10 —> 10/20 mg is not equal to the treatment effect of Lotrel 5/10 —> 5/20 mg.

The sample size is calculated to have statistical power of $\geq$ 80% for rejecting this two-sided null hypothesis at the 0.05 significance level, when the alternative hypothesis is true and the unknown true difference in MSDBP is at least 3.0 mmHg between Lotrel 5/10 —> 10/20 mg and Lotrel 5/10 —> 5/20 mg, assuming a standard deviation of 7.5 mmHg.

1.5 Dose and duration: patients received either 8 weeks of placebo, 2 weeks of 5/10 mg followed by 5/20 mg for 6 weeks, or 2 weeks of 5/10 mg followed by 6 weeks of 10/20 mg.

1.6 Study Procedure

Schematic diagram

Period	Washout	Single-blind placebo	Double-blind treatment			
			Randomization ⇓			
Visit		1	2	3	4	5
Treatment Week	-4	-2	0	2	4	8
Complete History/Physical Examination		X				
Interim/Final Physical Examination			X	X	X	X
Blood Pressure and Pulse Rate		X	X	X	X	X
Randomization			X			
12-Lead ECG		X				
Safety Laboratory Tests		X	X			X
Serum Pregnancy Test		X	X	X	X	X
Adverse Experiences			X	X	X	X
Concomitant Medications		X	X	X	X	X
Dispense Trial Medication		X	X	X	X	
Collect and Count Trial Medication			X	X	X	X
Termination Sheet						X

1.7 Protocol defined study hypotheses and efficacy endpoints: change from baseline in mean sitting diastolic blood pressure.

1.8 Secondary endpoints: change from baseline in mean sitting systolic blood pressure.

1.9 Disallowed concomitant medications

- Any other antihypertensive drug
- All antidepressant drugs, e.g., MAO inhibitors and tricyclics
- Antiarrhythmic drugs
- Psychotropic drugs, except for hypnotics and mild anxiolytic agents such as benzodiazepines, if these were used occasionally before the start of the trial.
- Estrogen replacement therapy, unless this has been used by the patient as maintenance for at least 3 months prior to entry into this trial.
- Hormonal contraceptives, including Norplant, must have been discontinued for at least one month prior to Visit 1.
- Sympathomimetic drugs such as those found in nasal decongestants, oral decongestants (pseudoephedrine and phenylpropanolamine) and bronchodilators (e.g., metaproterenol).
- Ergot preparations.

- The use of drugs in the last 6 months which are commonly hepatotoxic (e.g., methotrexate) or nephrotoxic (e.g., gentamicin).
- Thyroid medication unless this has been a stable maintenance replacement dose for the preceding 3 months.
- Antianginal medication of any kind including other calcium channel blockers, nitrates (orally, sublingually, or transdermally), or beta blockers.
- Any drug used for the treatment of heart failure, including digoxin, nitrates or angiotensin converting enzyme inhibitors.

1.10 Major protocol amendments

amendment #1: upper limit of diastolic blood pressure criterion (Visits 1 and 2) was reduced from 120 mm Hg to 1115 mm Hg.

amendment #2: patients with systolic blood pressure above 200 mmHg were excluded from study participation. Prohibited concomitant medications were changed to include antiarrhythmic drugs; any other antihypertensive drug; hormonal contraceptives, including Norplant@, must have been discontinued for at least one month prior to Visit 1; antianginal medication of any kind including other calcium channel blockers, nitrates (orally, sublingually, or transdermally), or beta blockers; serotonin reuptake inhibitors approved for treating obesity; other drugs which in the opinion of the investigator or the medical monitor could affect blood pressure.

2.0 Results

A total of 457 patients were screened and 386 were randomized and entry into the double blind treatment phase. There were 30 study sites, all located in the United States.

2.1 Patient disposition

Table below shows the outcome for all randomized subjects by treatment group.

	Lotrel 5/20 mg	Lotrel 10/20 mg	Placebo
No. randomized	127	125	134
Completed titration phase (Visit 3)	120	114	115
No. prematurely withdrawn during titration phase	7	11	19
No. prematurely withdrawn after titration phase	6	6	9
No. who completed study	114	108	106
No. in primary efficacy analysis	119	114	115
No. in safety analysis/lab	127/122	125/119	132/128

Patients who discontinued prematurely from the trial are shown below.

Total premature withdrawn	**13**	**17**	**28**
For adverse event	3	5	4
For abnormal lab	2	4	1
For lack of effect	1	0	8
For not meeting protocol criteria	2	1	7
For non compliance	2	3	2
For being lost to follow up	2	1	1
For dying	0	1	0
Other	1	2	5

More placebo patients withdrew compared to the 2 active treatment groups. Most placebo patients dropped out for lack of effect or not meeting protocol criteria. The drop outs for adverse events were close to being evenly spread out across treatment groups.

2.2 Demographics and baseline characteristics

Demographics for the study subjects, by treatment group, are shown below.

No. and (percent) of patients

	Lotrel 5/20 mg N=127	Lotrel 10/20 mg N=125	Placebo N=134
Male	58 (46)	70 (56)	72 (54)
Female	69 (54)	55 (44)	62 (46)
White	82 (65)	81 (65)	89 (66)
Black	35 (28)	33 (26)	36 (27)
Other	10 (8)	11 (9)	9 (7)
Less than 65 years of age	97 (76)	90 (72)	113 (84)
At least 65 years of age	30 (24)	35 (28)	21 (16)

Means and (ranges)

	Lotrel 5/20 mg N=127	Lotrel 10/20 mg N=125	Placebo N=134
Age: yrs	55 (22-77)	56 (27-78)	54 (25-78)
Height: inches	66 (58-77)	67 (57-80)	67 (59-77)
Weight: lbs	196 (116-329)	199 (101-326)	198 (119-390)

Nothing in the demographics appears unusual. The groups were well balanced.

2.2.1 Disease history

Summary of baseline disease characteristics is shown below.

	Lotrel 5/20 mg N=127	Lotrel 10/20 mg N=125	Placebo N=134
Mean duration of hypertension: yrs	9	10	10
% used antihypertension meds in past 3 months	79	80	78

Mean duration of hypertension was 9-10 years and more than three fourths of patients had been taking antihypertensive medication.

2.2.2. Duration on double blind medication

Days

	Lotrel 5/20 mg N=127	Lotrel 10/20 mg N=125	Placebo N=134
Mean duration (range) in DB phase	53.5	51.6	49.1

Mean duration of treatment was a bit longer for the active treatment groups compared to the placebo group.

2.3 Efficacy

2.3.1.Study discontinuations

The table below shows the number and percent of all premature study discontinuations.

	Lotrel 5/20 mg N=127	Lotrel 10/20 mg N=125	Placebo N=134
Discontinued during titration phase	7	11	19
Discontinued during post titration phase	6	6	9
Total discontinued	13	17	28

Reasons for discontinuation	Lotrel 5/20 mg N=13	Lotrel 10/20 mg N=17	Placebo N=28
Death	0	1	0
Adverse event	3	5	4
Abnormal lab	2	4	1
Lack of effect	1	0	8
Pt does not meet entry criteria	2	1	7
Non compliance	2	3	2
Lost to follow up	2	1	1
other	1	2	5

The placebo group had the highest number of dropouts.

2.3.2 Primary endpoint: change in mean sitting diastolic blood pressure from baseline at endpoint

Results are shown below.

Mean (SD) sitting diastolic blood pressure mmHg

	Lotrel 5/20 mg N=119	Lotrel 10/20 mg N=114	Placebo N=115
Baseline	100.3 (4.5)	100.5 (4.5)	101.2 (4.5)
Endpoint	85.6 (8.5)	84.8 (8.1)	95.8 (9.6)
Change from baseline at endpoint	-14.8 (7.6)	-15.7 (7.2)	-5.4 (8.0)
Treatment effect	-9.4	-10.3	-

While the treatment effects for the active groups were large, the difference between the active groups was only 0.9 mmHg.

Table 6. Summary results of the between-treatment analyses for change from baseline (Visit 2) in mean sitting diastolic blood pressure (mm Hg) at Endpoint and Visit 5

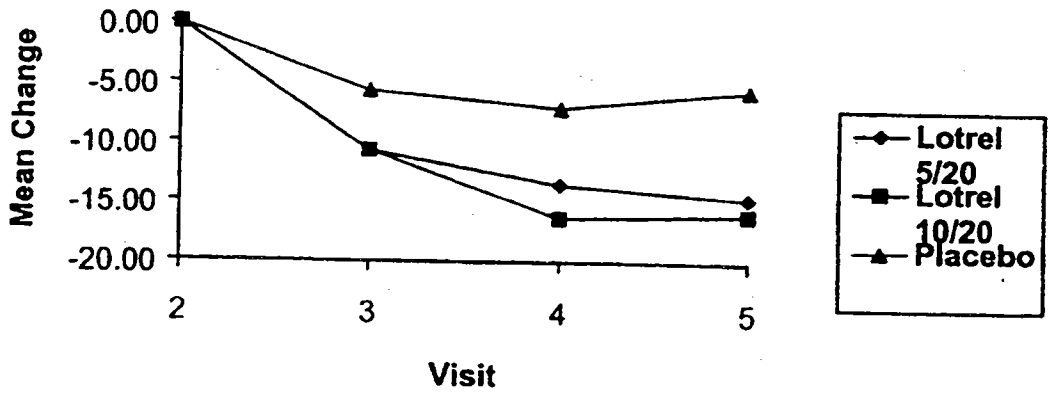
Comparison	Time	Least square estimate	p-value	95% confidence interval
"Lotrel" 10/20 vs. Lotrel 5/20	Endpoint	-1.3776	0.1896	(-3.44, 0.68)
	Visit 5	-1.8073	0.0876	(-3.88, 0.27)
"Lotrel" 10/20 vs. placebo	Endpoint	-10.5224	< 0.0001†	(-12.58, -8.47)
	Visit 5	-10.6530	<0.0001†	(-12.75, -8.56)
Lotrel 5/20 vs. placebo	Endpoint	-9.1448	<0.0001†	(-11.18, -7.11)
	Visit 5	-8.8458	<0.0001†	(-10.92, -6.77)

Source: Table 15.1-11.1-1
† Indicates a statistical significance at the level of 0.05.

Both doses were significantly better than placebo, but not significantly different from one another.

2.3.2.1 Effect by visit

Figure 2. Average change from baseline (Visit 2) in MSDBP (mm Hg) vs. visit by treatment group



By subgroups

Patients were stratified prior to randomization by race. The numbers of patients by race and treatment group are shown below.

No. of patients

	Lotrel 5/20 mg N=127	Lotrel 10/20 mg N=125	Placebo N=134
White	82	81	89
black	35	33	36
other	10	11	9

The placebo subtracted changes in mean sitting diastolic blood pressure by race are shown below.

Placebo subtracted change: mean sitting diastolic blood pressure (mmHg)

	Lotrel 5/20 mg	Lotrel 10/20 mg
White	-9.8	-10.0
black	-8.8	-11.4
other	-7.3	-9.0

Compared to the lower dose group, the higher dose group showed marginally better results in all race subgroups.

The placebo subtracted mean changes in mean sitting diastolic blood pressure for ages <65 and ≥ 65 were -9.3 and -7.6 mmHg, respectively, for the 5/20 mg group and -9.4 and –9.8 mmHg, respectively, for the 10/20 mg group.

The placebo subtracted mean changes in mean sitting diastolic blood pressure for males and females were -8.1 and -10.3 mmHg, respectively, for the 5/20 mg group and -9.1 and -11.7 mmHg, respectively, for the 10/20 mg group.

There seems to be no influence of race, gender, or age on blood pressure response with Lotrel.

2.3.3 Secondary endpoints: change in mean sitting systolic blood pressure from baseline at endpoint

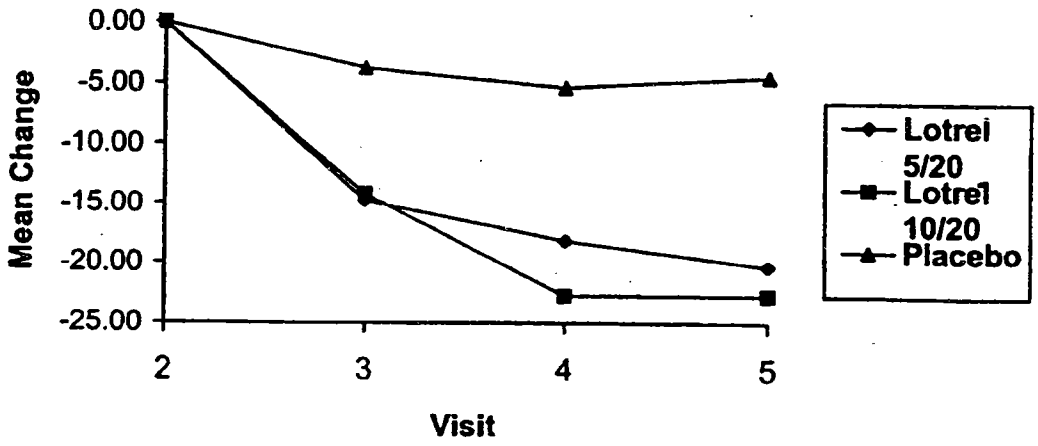
Mean sitting systolic blood pressure (mmHg)

	Lotrel 5/20 mg N=119	Lotrel 10/20 mg N=114	Placebo N=115
Baseline	153.2	155.7	152.0
Endpoint	132.8	133.6	147.4
Change from baseline at endpoint	-20.4	-22.1	-4.6
Treatment effect	-15.8	-17.5	--

The treatment effect for the active drugs was large, but the difference between the doses of Lotrel wasn't (1.7 mmHg).

By visit

Figure 4. **Average change from baseline (Visit 2) in MSSBP (mm Hg) vs. visit, by treatment group**



APPEARS THIS WAY
ON ORIGINAL

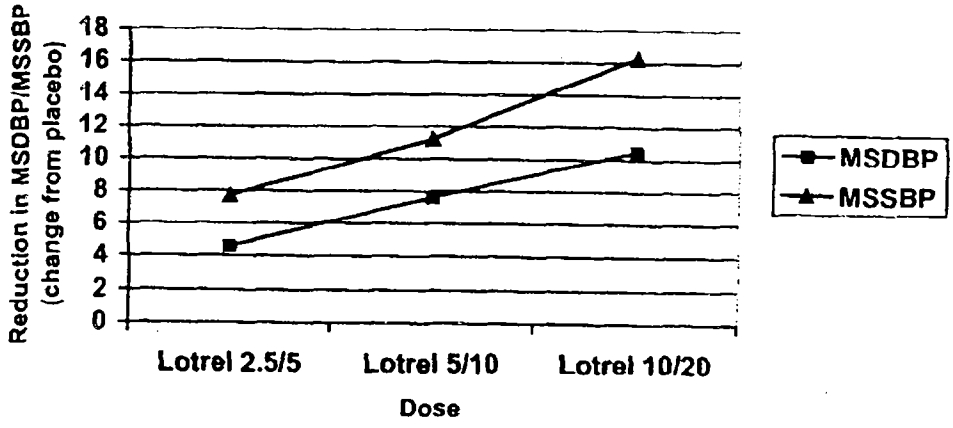
Dosing response

The sponsor conducted a meta-analysis using data from the original Lotrel NDA to assess dose response with data from doses that were a 1:2 ratio (amlodipine:benazepril). The table and figure below show placebo subtracted mean change from baseline for sitting diastolic (MSDBP) and systolic (MSSBP) blood pressure.

Table 10. Placebo-Subtracted MSDBP and MSSBP at Endpoint

Dose	Protocol	MSDBP at Endpoint (Least Squares Change)	MSSBP at Endpoint (Least Squares Change)
2.5/5	03	-4.7	-7.8
	15	-4.5	-7.6
	Pooled	-4.6	-7.7
5/10	03	-7.8	-11.6
	05	-7.6	-10.7
	Pooled	-7.7	-11.2
10/20	104	-10.5	-16.3

Figure 3. Meta-Analysis: Dose Response-Lotrel 2.5/5, 5/10, and 10/20



The changes at endpoint for placebo subtracted diastolic and systolic blood pressures were larger with higher doses compared to lower doses, suggesting a positive dose response.

3.0 Safety

Serious safety including deaths, serious adverse events and withdrawals for adverse events.
No. of patients

	Lotrel 5/20 mg N=125	Lotrel 10/20 mg N=127	Placebo N=132
Deaths	0	1	0
Serious adverse events	4	3	3
Study discontinuations for safety^	6	10	7
-for lab abnormalities	3	4	3
-for adverse event	3	5	4

^adverse event or lab abnormality or death

There was 1 reported patient death was a 77 year old white male (Lotrel 10/20 mg) with type 2 diabetes mellitus who had a myocardial infarction and died on double blind treatment day 54.

APPEARS THIS WAY
ON ORIGINAL

Deaths, discontinuations for safety, serious adverse events

Lotrel 10/20	
death	
pt#48	Death attributed to MI
Discontinuations	
Pt#99	Glucose elevation
Pt#318	Elevated LFTs (history of hepatitis)
Pt# 449	Elevated glucose
Pt# 460	Elevated LFTs (elevations at baseline)
Pt#28	Flushing, skin discoloration, edema
Pt#270	Cough, abnormal asculatory findings, face edema
Pt#464	Palpitation, arrhythmia, fatigue
Pt#485	Dyspepsia
Pt#302	Dizziness, abnormal thinking, edema, eye irritation, micturition frequency
serious adverse events	
Pt #311	Basal cell carcinoma
Pt#328	Hysterectomy for menorrhagia
Pt#387	cholelithiasis
Lotrel 5/20 mg	
discontinuations	
Pt#173	Elevated creatinine
Pt#232	Nausea, vomiting
Pt# 248 +	Angioedema
Pt #342	Elevated LFTs
Pt#466 +	Supraventricular tachycardia
Pt #498	Glucose elevation
serious adverse events	
Pt #173	Carotid stenosis
Pt #232	Abdominal pain, diarrhea, adhesiolysis, oophorectomy
Placebo	
discontinuations	
Pt#40	Elevated LFTs
Pt# 128	Elevated glucose
Pt#166	Lip swelling, laryngitis, hives,
Pt# 282 +	Congestive heart failure
Pt# 381	Elevated glucose
Pt#373	Rash, pruritus, edema
Pt#88	weight increased, edema
serious adverse events	
Pt #166	rash
Pt #483	Spontaneous abortion

+also listed as a serious adverse event

All adverse events

The adverse events reported by at least 2 patients in at least 1 Lotrel treatment group and were reported by at least 1% more often in a Lotrel group compared to placebo group are shown below. The last column shows the placebo subtracted percent of patients randomized to Lotrel 10/20 and reported a selected event.

No. and (percent) of patients

	Lotrel 5/20 mg N=127	Lotrel 10/20 mg N=125	Placebo N=132
Total with at least 1 AE	79 (62.2)	77 (61.6)	80 (60.6)
Coughing	16 (12.6)	11 (8.8)	5 (3.8)
Edema^	10 (7.8)	18 (14.4)	11 (8.3)
Dyspepsia	0	5 (4.0)	0
Leg cramps	3 (2.4)	4 (3.2)	0
Dizziness	3 (2.4)	8 (6.4)	5 (3.8)
Epistaxis	0	3 (2.4)	0
Nausea	4 (3.2)	4 (3.2)	2 (1.5)
Anemia	3 (2.4)	0	1 (0.8)
Thirst	2 (1.6)	0	0
Back pain	7 (5.5)	1 (0.8)	4 (3.0)
Anxiety	3 (2.4)	2 (1.6)	1 (0.8)
Hypoesthesia	3 (2.4)	0	1 (0.8)
Pharyngitis	6 (4.7)	3 (2.4)	4 (3.0)
Bruising	4 (3.2)	0	0
Skin disorder	2 (1.6)	0	0
Vertigo	2 (1.6)	0	0
Procedure:female reproductive	2 (1.6)	1 (0.8)	0
Viral infection	6 (4.7)	4 (3.2)	4 (3.0)

^includes dependent, legs, peripheral

As expected with an ACE inhibitor and a calcium channel blocker combination, coughing and edema (excluding facial edema) were commonly reported adverse events in the active treatment group.

The placebo subtracted incidence rates for the higher dose groups for selected adverse events are shown below.

Incidence rate—placebo subtracted

	Lotrel 10/20 % Placebo subtracted
Total with at least 1 AE	1.0
Coughing	5.0
Edema	6.1
Dyspepsia	4.0
Leg cramps	3.2
Dizziness	2.6
Epistaxis	2.4
Nausea	1.7

The placebo subtracted incidence rates for coughing[1] were 8.8% and 5% for the 5/20 and 10/20 mg dose groups, respectively, and the placebo subtracted incidence rates for edema[2] were -0.5% and 6.1%, respectively.

Other events occurring more often with a Lotrel 10/20 mg compared to the lower dose in study 104 include dyspepsia, leg cramps, dizziness, and epistaxis. From this subgroup of events, only dizziness was labeled as "drug related" in the original Lotrel submission even though in that database it was reported less often by patients on Lotrel compared to patients on placebo.

Adverse events included in the current Lotrel label

The incidence rates for reporting selected adverse events in the original Lotrel NDA are shown below.

Percent of patients

	Benazepril/amlodipine N=760	Placebo N=408	Placebo subtracted
Cough	4.9	1.2	3.7
Headache	11.1	16.9	-5.8
Dizziness	3.3	3.2	-0.1
Any edema	2.8	2.9	-0.1

Section 8 pages 97-98 of ISS vol 34

Only cough stands out as being an adverse event that is associated with active drug treatment in the original NDA.

Adverse events by gender

The placebo subtracted rates for selected adverse events reported by the Lotrel 10/20 mg group in protocol 104 and in the original NDA are shown below by gender.

Percent of patients reporting event—placebo subtracted

	Lotrel 10/20 Protocol 104#		Original NDA+	
	Male N=70	Female N=55	Male N=329	Female N=431
Headache	-8.1	3.9	-5.0	-7.6
Edema (pooled)	5.9	8.3	-0.6	-0.3
Cough	1.5	9.4	4.1	3.0
dizziness	1.5	3.9	1.8	-1.7

#from table 6 of ISS vol1
+all doses combined;

Unlike the original NDA, the placebo subtracted incidence rates in protocol 104 for headache, edema, cough and dizziness are higher in the female patients compared to the male patients.

[1] Comparable rate in the original NDA was 3.1% (amlodipine 2.5-5 mg/benazepril 10-20 mg)
[2] Comparable rate in the original NDA was –0.1%

Adverse events by race

The placebo subtracted rates for selected adverse events reported by the Lotrel 10/20 mg group is shown below by race (not including the "other" category because of too few patients).

Incidence rate-placebo subtracted

	Lotrel 10/20 mg	
Adverse event	White N=81	Black N=33
Headache	5.0	-17.3
Pooled edema	11.7	-2.4
Cough	6.5	6.2
dizziness	4.2	0.1

Sample sizes for the white and black categories are slim. That said, there was much more reporting of "pooled" edema in white patients compared to black.

Heart rate

Heart rate reported for protocol 104 is shown below.

Mean sitting heart rate (bpm)

	Lotrel 5/20 mg N=119	Lotrel 10/20 mg N=114	Placebo N=115
Baseline	73.9	72.3	72.2
Endpoint	74.2	75.0	72.7
Change from baseline at endpoint	0.7	2.8	0.5
Treatment effect	0.2	2.3	--

The effect of Lotrel on heart rate, if any, is small.

Laboratory values

The tables below show the number and percent of patients by treatment group who had abnormal changes in chemistry and/or hematology values.

Table No: 15.1-12.4-3 Number of patients with specified percent or absolute change from baseline for laboratory tests (All safety analyzable patients)

Blood Chemistry

	Lotrel 5/20		Lotrel 10/20		Placebo	
	N	%	N	%	N	%
Calcium, Total, Serum (mg/dL)						
Total Patients	117		114		122	
> 10 % Increase	3	(2.5%)	2	(1.7%)	0	(0.0%)
> 10 % Decrease	1	(0.8%)	0	(0.0%)	2	(1.6%)
Calculated BUN (mg/dL)						
Total Patients	121		117		128	
> 50 % Increase	9	(7.4%)	6	(5.1%)	3	(2.3%)
Chloride (mEq/L)						
Total Patients	117		114		122	
> 10 % Increase	1	(0.8%)	0	(0.0%)	0	(0.0%)
Creatinine, Plasma or Serum (mg/dL)						
Total Patients	117		114		122	
> 50 % Increase	3	(2.5%)	0	(0.0%)	1	(0.8%)
Phosphorus (mg/dL)						
Total Patients	117		114		122	
> 50 % Increase	1	(0.8%)	1	(0.8%)	0	(0.0%)

	Lotrel 5/20		Lotrel 10/20		Placebo	
	N	%	N	%	N	%
Bilirubin, Serum (mg/dL)						
Total Patients	117		114		122	
> 100 % Increase	5	(4.2%)	2	(1.7%)	2	(1.6%)
Glucose (mg/dL)						
Total Patients	117		114		122	
> 50 % Increase	1	(0.8%)	1	(0.8%)	2	(1.6%)
Potassium (mEq/L)						
Total Patients	117		114		122	
> 20 % Increase	6	(5.1%)	4	(3.5%)	3	(2.4%)
> 20 % Decrease	0	(0.0%)	1	(0.8%)	1	(0.8%)
Sodium (mEq/L)						
Total Patients	117		114		122	
> 5 % Decrease	1	(0.8%)	2	(1.7%)	1	(0.8%)
Uric Acid, Serum (mg/dL)						
Total Patients	117		114		122	
> 50 % Increase	2	(1.7%)	0	(0.0%)	1	(0.8%)

As expected, more patients on Lotrel had ≥ 20% increase over baseline values in potassium compared to patients on placebo (placebo subtracted rates were 2.7% and 1.1% for Lotrel 5/20 mg and 10/20 mg, respectively). BUN elevations of >50% over baseline occurred more frequently in the Lotrel groups as well (placebo subtracted rates were 5.1% and 2.8% for Lotrel 5/20 mg and 10/20 mg, respectively). Biliubin increases of 100% were more frequent in the Lotrel 5/20 mg group (placebo subtracted rate of 2.6%) compared to Lotrel 10/20 mg (0.1%). Overall, the increase in the dose of amlodipine did not affect laboratory values

There were 3 Lotrel patients and 1 placebo patient who discontinued study drug because of elevated LFTs. The patients who were on active therapy are discussed below.

Lotrel 10/20 Patient 318: 45 years old, white, male with history of hepatitis. At the time of randomization, the patient's ALT level was 96 U/L and AST was 34 U/L. Trial drug was permanently discontinued after 14 days of double-blind treatment. On the day following trial drug discontinuation, the patient's ALT remained elevated (79 U/L) while the AST value remained normal (21 U/L).

Lotrel 10/20 Patient 460: 37 years old, white, male entered the study with an elevated ALT (208 U/L) and AST (163 U/L) and alkaline phosphatae (250 U/L). Study drug was permanently discontinued after 3 days of double-blind treatment. Eighteen days later, ALT and AST remained elevated (158 U/L and 93 U/L, respectively, as well as alkaline phosphatase (223 U/L.

Lotrel 5/20 mg Patient 342: 66 year old, black, female elevated ALT (42 U/L), elevated alkaline phosphatase (535 U/L), and elevated AST (51 U/L) at study entry. Study drug was permanently discontinued after 15 days of double-blind treatment. Concomitant medication included phenobarbital.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Maryann Gordon
1/9/02 02:17:03 PM
MEDICAL OFFICER

NDA#20,364
Drug name: Lotrel
Sponsor: Novartis
Medical reviewer: Maryann Gordon, MD

RE: financial disclosure

I have reviewed the financial disclosure submitted by the sponsor and dated 4-12-02. The sponsor claims that no investigator who participated in study 104 entered into any financial arrangement with them "whereby the value of compensation to the investigator could be affected by the outcome of the study."

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Maryann Gordon
4/17/02 06:42:03 AM
MEDICAL OFFICER