CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)
20-364/SE8-016

Trade Name: Lotrel Capsules

Generic Name(s): (amlodipine benazepril)

Sponsor: Novartis Pharmaceuticals Corp.

Approval Date: June 20, 2002

Indication: Provides for a new, higher dosage strength that combines 10 mg of amlodipine with 20 mg of benazepril

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-364/SE8-016

Correspondence

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	(973) 781-3590
Attention:	Carl Schlotfeldt
Company Name:	Novartis Pharmaceuticals Corporation
Phone:	(973) 781-3570
Subject:	NDA 20-364
Date:	June 21, 2002
Pages including this sheet:	3

From: **Denise M. Hinton**
Phone: **301-594-5312**
Fax: **301-594-5494**

MESSAGE CONFIRMATION

06/21/02 11:46
ID=FDA CDER DCRDP

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DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S.CODE
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: November 30, 1995.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Ciba Pharmaceuticals Division, CIBA-GEIGY Corporation

2. DATE OF SUBMISSION
February 6, 1997

3. ADDRESS *(Number, Street, City, State and Zip Code)*
556 Morris Avenue
Summit, New Jersey 07901

4. TELEPHONE NUMBER *(Include Area Code)*
(908) 277-5315

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
benazepril HCl plus amlodipine besylate (CGS-24267A)

6. IND NUMBER *(If previously assigned)*
[redacted]

7. INDICATION(S) *(Covered by this submission)*
Hypertension

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☒ OTHER Phase IV *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 312)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

benazepril:
IND [redacted]
IND [redacted]
NDA 19-851

amlodipine:
IND [redacted]
NDA 19-787

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER: 046

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):	INFORMATION AMENDMENT(S):	IND SAFETY REPORT(S):
☒ NEW PROTOCOL	☐ CHEMISTRY/MICROBIOLOGY	☐ INITIAL WRITTEN REPORT
☐ CHANGE IN PROTOCOL	☐ PHARMACOLOGY/TOXICOLOGY	☐ FOLLOW-UP TO A WRITTEN REPORT
☐ NEW INVESTIGATOR	☐ CLINICAL	

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.34(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHANGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

12

CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☒ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

I agree not to begin clinical investigations until 30 days after FDA'a receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that compiles with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE
Adrian L. Birch Executive Director, DRA	for: Adrian L. Birch
18. ADDRESS *(Number, Street, City, State and Zip Code)*	**19. TELEPHONE NUMBER** *(Include Area Code)* / **20. DATE**
556 Morris Avenue Summit, New Jersey 07901	(908) 277-5315 / 2/6/97

(WARNING: A willfully false statement is a criminal offense. U.S.C Title 18, Sec. 1001.)

Fax

Novartis Pharmaceuticals Corporation
59 Route 10 East
East Hanover, NJ 07936

TO		FROM	
Name:	Ms. Denise Hinton, Project Manager	Name:	Carl Schlotfeldt
Company:	FDA, HFD-110	Dept.:	DRA
Location:	Rockville, MD	Location:	Bldg 122, room N306
Country:		Fax No.:	973-781-3590
Fax No.:	301-594-5494	Phone No.:	973-781-3570
Total pages	5	Date:	July 2, 2002

Reference: NDA 20-364, Lotrel®

Dear Ms. Hinton,

This is in response to your telephone inquiry regarding the FDA 1571 associated with the submission of Lotrel protocol 104 to IND [redacted] Attached are copies of the coverletter and 1571 dated Feb. 6, 1997. At that time we were still using the Ciba Geigy Corporation name on our stationary. Shortly thereafter, on Feb 12, 2002, via serial number 047, we filed to this IND a letter documenting transfer of ownership to Novartis Pharmaceuticals Corp. Our copy of the letter is in archives but it can be retrieved if needed.

Please call me at 973-781-3570 if you have any further questions or comments on the matter.

Carl Schlotfeldt
Associate Director DRA

Pharmaceuticals Division

ciba

Ciba-Geigy Corporation
Summit, New Jersey 07901

February 6, 1997

IND [redacted]
Lotrel®
(Amlodipine besylate/benazepril HCl)

IND Amendment Number 046
•Protocol Amendment - new protocol

Center for Drug Evaluation and Research
Food & Drug Administration
Document Control Room 16B-30
5600 Fishers Lane
Rockville, MD 20857

Attention: Dr. Raymond J. Lipicky, MD. Director
Division of Cardio-Renal Drug Products (HFD-110)

Dear Dr. Lipicky,

We refer to our IND [redacted] for Lotrel (amlodipine besylate/benazepril HCl). This amendment consists of a new phase IV protocol entitled:

> **Protocol 104** - A Randomized, Double-Blind, Placebo-Controlled, Forced-Titration, Parallel Trial Comparing the Safety and Efficacy of Lotrel 5/20 mg Once Daily to Lotrel 10/20 mg Once Daily in Patients with Essential Hypertension

Attached is a copy of protocol 104 and a blank copy of the case record form. Also attached are copies of protocol amendments 1 and 2. Amendment 1 modifies the diastolic blood pressure criteria (115 mmHg maximum instead of 120 mmHg). Amendment 2 establishes an upper limit of 200 mmHg for systolic blood pressure. These amendments address concerns raised by the IRB.

Investigators

The following investigators will participate in protocol 104.

1. 2.

3. 4.

5. [redacted]

For each of the above new investigators attached are copies of the signed form FDA 1572, curriculum vitae, patient informed consent form and IRB approval letter.

If you have any questions or comments concerning the above information and documentation please contact Mr. Carl Schlotfeldt, Associate Director DRA at 908-277-5315.

Very truly yours,

CIBA Pharmaceutical Co.
Division of CIBA-GEIGY Corp.

Carl Schlotfeldt

for Mr. Adrian Birch
Executive Director
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

September 5, 2000

Raymond J. Lipicky, MD, Director
Division of Cardio-Renal Drug
Products/HFD-110
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20852

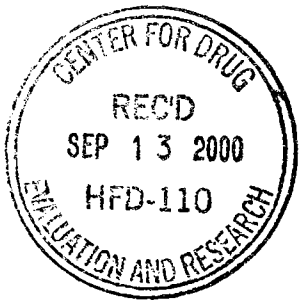
NDA 20-364
Lotrel® (amlodipine and benazepril hydrochloride)

Dear Dr. Lipicky:

We refer to our NDA 20-033 for Lotrel. This is a follow up to our previous submission dated August 3, 2000 in which we requested a meeting with FDA.

Enclosed are our minutes of the meeting which took place on August 22, 2000. Thank you again for giving us the opportunity to meet and obtain FDA feedback on this matter.

You can reach me at (973) 781-3570 if you have a question or comment on the above.



Sincerely,

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

D.K. per RL.

CS/kp
Attachment
Submitted in duplicate

Desk copy: Z. McDonald for D. Roeder, HFD-110

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	September 5, 2000
TELEPHONE NO. (*Include Area Code*)	FACSIMILE (FAX) Number (*Include Area Code*)
((973) 781-3570	**(973) 781-3590**
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*):	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE
59 Route 10 **East Hanover, New Jersey 07936-1080**	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **20-364**

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY	
amlodipine besylate/benazepril HCl	**Lotrel®**	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)		CODE NAME (*If any*)
DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsules	**2.5/10 mg, 5/10 mg, 5/20 mg**	**P.O.**

(PROPOSED) INDICATION(S) FOR USE:

Hypertension

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

REASON FOR SUBMISSION
meeting minutes

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Application, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (*Check all that apply*)

	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606 and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact law.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowlegde are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Carl Schlotfeldt	**Carl Schlotfeldt, Associate Director** **Drug Regulatory Affairs**	9/5/00

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
59 Route 10 **East Hanover, New Jersey 07936-1080**	**(973) 781-3570**

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.