CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-364/SE8-016

Administrative Documents

Item 13
Time Sensitive Patent Information
Pursuant to 21 C.F.R. 314.53
for
NDA 20-364

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	Lotrel®
Active Ingredient:	Amlodipine and benazepril HCl
Strengths:	2.5/10 mg, 5/10 mg, 5/20 mg and 10/20 mg
Dosage Form:	Capsules for oral administration

U.S. Patent Number:	U.S. 4,410,520
Expiration Date:	August 11, 2003
Type of Patent:	Drug Substance, Drug Product and Method of Use
Name of Patent Owner:	Novartis Corporation

U.S. Patent Number:	U.S. 4,572,909
Expiration Date:	July 31, 2006
Type of Patent:	Drug Substance, Drug Product and Method of Use
Name of Patent Owner:	Pfizer, Inc.

U.S. Patent Number:	U.S. 4,879,303
Expiration Date:	March 25, 2007
Type of Patent:	Drug Substance, Drug Product and Method of Use
Name of Patent Owner:	Pfizer, Inc.

U.S. Patent Number:	U.S. 6,162,802
Expiration Date:	December 19. 2017
Type of Patent:	Method of Use and Drug Product
Name of Patent Owner:	Novartis Corporation

EXCLUSIVITY SUMMARY for NDA # 20-364 SUPPL # -16

Trade Name Lotrel Generic Name amlodipine and benazepril HCl capsules

Applicant Name Novartis Pharmaceuticals Corportation HFD- 110

Approval Date June 20, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE8

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_ _/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-364, Lotrel Capsules

NDA # 19-851 Lotensin

NDA # 20-033, Lotensin HCT NDA # 19-787, Norvasc

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Protocol 104

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # ___Protocol 104

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 | *IND # [redacted] YES /__/* | *NO /X/ Explain:*

Ciba-Geigy Corporation is listed as the sponsor on the February 6, 1997 FDA Form 1571, however, the corporation merged with Novartis in January 1997. On February 12, 1997 a letter was filed to IND [redacted] documenting transfer of ownership to Novartis Pharmaceuticals Corporation.

Investigation #2 | IND # _____ YES /___/ | NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 | YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

Investigation #2 | YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

Signature of Preparer: /S/ Date: July 2, 2002
Denise M. Hinton

Title: Regulatory Health Project Manager

Signature of Office or Division Director Date

/S/

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Doug Throckmorton
7/10/02 03:59:17 PM

DEBARMENT CERTIFICATION

NOVARTIS PHARMACEUTICALS CORPORATION hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or (b) of the Federal Food, Drug and Cosmetic Act, in connection with this supplementary application for Lotrel® 10/20 mg capsules, NDA 20-364.

Signed Carl Schlotfeldt Date 6/14/01

Carl Schlotfeldt
Associate Director
Drug Regulatory Affairs

debar.doc

Locicero, Colleen L

From: Throckmorton, Douglas C
Sent: Friday, May 31, 2002 12:54 PM
Haffer, Andrew; Gordon, Maryann; Locicero, Colleen L
Subject: Lotrel 10/20

Andy, I've gone over the labeling you highlighted and read Maryann's response, and I agree with her as regards the edema. She's correct in pointing out we don't know precisely the rate of edema for the 10/20 product is less than the amlodipine 10 mg alone, but the data are in general agreement with the statements we've placed in the label about the utility of adding benazapril to amlodipine if edema is a problem. I don't see a need for modification of the label beyond those that we've proposed in response to the most recent supplement. Thanks, DCT

Locicero, Colleen L

From: Gordon, Maryann
Sent: Wednesday, May 29, 2002 2:01 PM
To: Haffer, Andrew
Cc: Throckmorton, Douglas C; Locicero, Colleen L; Stockbridge, Norman L
Subject: RE: Lotrel 10/20mg supplement and edema

Dear Andy,

Attached is my response to your memo.

labelandy20364.doc

Maryann

-----Original Message-----
From: Haffer, Andrew
Sent: Thursday, May 23, 2002 3:29 PM
To: Locicero, Colleen L
Cc: Throckmorton, Douglas C; Gordon, Maryann; Chong, Barbara; Cropp, Cheryl
Subject: Lotrel 10/20mg supplement and edema

Attached is a memo regarding proposed changes to the PI for Lotrel.

<< File: edema comments.doc >>

Recommendation:
I do not support your conclusion that the language in the package label for Lotrel be changed as indicated in your memo dated May 23, 2002.

The underlying reason for using Lotrel (amlodipine/benazepril combination) is the occurrence of less edema compared to using amlodipine alone. As far as I can tell (and with little empirical data with the 10/20 mg dose), this interpretation remains true with the 10/20 mg dose. Therefore, I have no objection to keeping the statements in the proposed package label that you had questioned in your review.

Introduction
The table from the amlodipine label and shown below outlines the rate of edema for different doses of amlodipine monotherapy and placebo.

Adverse Event	2.5 mg N=275	5.0 mg N=296	10.0 mg N=268	Placebo N=520
Edema	1.8	3.0	10.8	0.6
Dizziness	1.1	3.4	3.4	1.5
Flushing	0.7	1.4	2.6	0.0
Palpitation	0.7	1.4	4.5	0.6

The placebo subtracted rates are 1.2%, 2.4%, 10.2% for amlodipine 2.5, 5.0 and 10 mg, respectively.

The Lotrel label states: "The incidence of edema was statistically greater in patients treated with amlodipine monotherapy than in patients treated with the combination." Although there are no data showing this to be true for the 10/20 mg dose because study 104 did not have an amlodipine monotherapy arm, there is no reason to think that it is not true.

The rate of edema (includes dependent, legs, and peripheral) reports for study 104 are shown below.

No. and (percent) of patients reporting edema

Event	Lotrel 5/20 mg N=127	Lotrel 10/20 mg N=125	Placebo N=132
Edema	10 (7.8)	18 (14.4)	11 (8.3)

Placebo subtracted rates –0.5% and 6.1% for Lotrel 5/20 and Lotrel 10/20, respectively.

Unsophisticatedly, one can say that the placebo subtracted rate of edema reporting for Lotrel 10/20 mg (6.1%), is less than the placebo subtracted rate for amlodipine 10 mg (10.2%). Although this is not a reliable method of comparison, it does not refute and, indeed, does support the premise that the use of the combination causes less edema compared to the same dose of amlodipine.

FDA Trip Report

August 22, 2000

Lotrel NDA 20-364

Novartis participants: Dr. Malcolm MacNab, Vice President Clinical Research, Dr. Tom Chiang, Biostatistics and Mr. Carl Schlotfeldt, Regulatory Affairs

FDA participants: Dr. Raymond Lipicky, Director Division of Cardio-Renal Drug Products and Dr. Norman Stockbridge, Medical Review Officer in Cardio-Renal

Executive Summary

This meeting was requested by Novartis to discuss a new higher strength of Lotrel, consisting of amlodipine 10 mg plus benazepril 20 mg. In advance of the meeting we provided to the FDA participants a meeting request letter dated August 3, 2000 with accompanying briefing materials. These materials included the results of a completed clinical trial, protocol 104, comparing the safety and efficacy of "Lotrel 10/20" (administered as 2 capsules of Lotrel 5/10) to Lotrel 5/20 and placebo. Also included was a summary of data in the Lotrel NDA to demonstrate how the results from protocol 104 compare. In reply to this request, Dr. Lipicky agreed to meet us [redacted] rather than postpone the meeting until his return to his FDA office in Rockville, MD.

Agreement was reached on the following key points:

- A dose response has been demonstrated for the new higher strength of Lotrel
- Stability and bioequivalence studies (which we had planned to do) are basically all that is needed for an SNDA
- Pooled safety data (protocol 104 with the Lotrel NDA database) is not necessary as long as the safety tables in the report for 104 are of similar format to those in the NDA.

Discussion

Mr. Schlotfeldt opened the meeting by explaining that our reason for introducing a new higher strength of Lotrel is in response to medical need for a more efficacious dose for some patients. We have performed a study (protocol 104) comparing the new strength to the current highest dose and placebo. Both active treatment arms beat placebo and the differences were statistically significant. Also, the mean reduction in BP (both diastolic and systolic) for Lotrel 10/20 was greater than that for Lotrel 5/20 (this difference was not statistically significant).

We reviewed the data contained in the briefing materials in order to show the FDA representatives that the dose response data in protocol 104 fit nicely with the data contained in the original NDA. Dr. Lipicky agrees that a dose response for Lotrel 10/20 has been demonstrated. He pointed out that since the components of the new dose are within the ranges of approved doses for both monotherapies he does not see any major issue with the approval of the fixed dose combination. He asked if we had done an analysis of the incidence of edema. We showed him representative safety data from protocol 104 and he agreed that the higher dose appears to be safe. He sees no benefit to us in performing a retrospective subset analysis of the dose response data in protocol 104 (e.g. patients whose baseline BP is

above 105 mmHg) because a dose response has been adequately demonstrated in the overall population in this study.

We were reminded of the need to perform a bioequivalency study for the new dosage form to show that it is equivalent to the component drugs and also to perform the necessary stability studies. We informed them that we had planned to do both.

We asked if they agree that it is not necessary for us to pool the safety data from protocol 104 together with the Lotrel NDA safety database. They agreed that this is not necessary as long as the data in protocol 104 is analyzed and presented in a way that allows direct comparison to the NDA safety database (similar displays of safety data).

We discussed how the clinical data for the new strength of Lotrel would appear in product labeling. We agreed that changes will be minor in this case. In the Pharmacodynamics subsection (para 9) and in Dosage and Administration section (para 1, second sentence) of the package insert, we will need to broaden the descriptions of the range of amlodipine doses studied in combination with benazepril.

Dr. Lipicky asked .

We thanked them for their feedback. This concluded the meeting.

Minutes prepared by: Carl Schlotfeldt, Associate Director DRA

Date: September 1, 2000

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
Division of Cardio-Renal Drug Products

Public Health Service

Memorandum

DATE : February 28, 2002

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110 /S/

SUBJECT: NDA 20-364/SE8-016, amlidipine/benazepril, Novartis

TO : NDA 20-364 NDA File

The treatment of hypertension frequently necessitates prescribing more than a single entity for the control of hypertension in an individual patient. Fixed-dose combination antihypertensive drug products are offered mainly as convenience products (one pill instead of two). Such is the case for the Lotrel®, however, in the data from the original NDA showed that benazepril decreased the edema associated with use of amlodipine. Thus, in the Dose Titrated by Clinical Effect section of DOSAGE and ADMINISTRATION it is noted that utilization of Lotrel® might be appropriate even if blood pressure is adequately controlled be amlodipine alone but problems with edema are complicate management. The approved PI says, " ...In patients whose blood pressure are adequately controlled with amlodipine but who experience unacceptable edema, combination therapy may achieve similar (or better) blood-pressure control without edema...".

Missing from the dosage forms marketed (prior to this supplement) was a dosage form that contained 10 mg of amlodipine. Supplement SE8-016, provide this dosage form and appropriately add to the marketed dosage strengths of this fixed-dose combination product.

The major feature of study 104 is that the doses of 10 mg amlodipine and 20 mg benazepril where significantly better than placebo ($p < 0.0001$), consequently it is approvable provided that there are no major chemistry or biopharm issues. It does not appear, to me, that there are any other pertinent factors to consider.

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel (301) 594-5327, FAX (301) 594-5494

Memorandum

DATE: 4.16.02

FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

SUBJECT: NDA 20-364/SE8-016,
NAME OF DRUG: Amlodipine/Benazapril (Lotrel®)
SPONSOR: Novartis Pharmaceuticals Corporation

DOCUMENTS USED FOR MEMO:

1. Memo from Raymond Lipicky, dated 2.28.02.
2. Chemistry Review by Nallaperumal Chidambaram, dated 2.27.02.
3. Clinical Pharmacology and Biopharmaceutics Review Elena Mishina, dated 3.12.02.
4. Medical Review by Maryann Gordon, dated 1.9.02.
5. Statistical Review by Valeria Freidlin, dated 1.14.02.
6. _____

CONCLUSIONS

This memorandum constitutes the secondary review for the named supplement as well as the memorandum of approvability for the proposed marketing of the amlodipine 10/ benazapril 20 mg dose of lotrel. The remaining issues relate to agreement between the Agency and the sponsor on labeling. _____

BACKGROUND

The current supplement proposes the addition of a combination of 10 mg of amlodipine with 20 mg of benazapril to the available dosage forms of lotrel (2.5/5, 5/10 and 5/20 of amlodipine/benazapril respectively).

CHEMISTRY

As noted in the chemistry review this drug product was produced through the _____ in the capsules. The lotrel 5/20 dosage will be supplied as a purple/pink opaque size 1 capsule with Lotrel 0364 printed on the cap in black ink with two white bands on the body. The changes recommended by Chemistry to the last paragraph of the 'Description' section (see review) were accepted by the sponsor. Pending the provision of a final printed label reflecting these changes, Chemistry recommended approval.

PHARMCOLOGY TOXICOLOGY

There was no Pharm-Tox review for this supplemental application.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The sponsor submitted bioequivalence testing and in vitro dissolution specifications, comparing the test formulation used in the clinical study (see below) with the to be marketed formulation. The two formulations were bioequivalent for Cmax and AUC for amlodipine and the active benazeprilat metabolite, but not the benazapril parent compound (which was equivalent by AUC but not Cmax). As the metabolite is more active, and the parent is quickly converted, this failure is of no significant clinical consequence. The Biopharm reviewer stated that 'the application is acceptable for meeting the recommendations of the Office of Clinical Pharmacology and Biopharmaeutics.'

MEDICAL/STATISTICAL REVIEW

The sponsor submitted a single randomized, double-blind, placebo-controlled, forced titration, parallel group study comparing amlodipine/benazapril 5/10, 10/20 and placebo (three groups). Patients in the benazapril 10/20 group were first titrated to the 5/10 dose, so that patients received the three different doses of study drug for a total of 6 weeks of the 8 weeks on study drug. Of the 386 randomized patients with essential hypertension, 328 completed the 8 weeks of therapy.

Efficacy

As summarized below, the lotrel 10/20 had a larger mean effect on blood pressure than did lotrel 5/20, but this difference was not significant per the primary analysis (change from baseline in mean sitting diastolic blood pressure) in the ITT population. Similar results were seen when systolic blood pressure was examined.

Change from Baseline for sitting diastolic blood pressure at endpoint[a].

	Mean Change from Baseline (mm Hg)[a]	p-Value versus Placebo	p-Value versus Lotrel 10/20
Placebo	-5.4	---	<0.0001
Lotrel 5/20	-14.8	<0.0001	0.19
Lotrel 10/20	-15.7	<0.0001	--

a. From Statistical Review, table 2 and 3.

The trial population was stratified for race prior to randomization. Per the Medical Reviewer, compared to the lotrel 5/20 mg group, the lotrel 10/20 group showed marginally better results in all race subgroups. Overall, no influence of race, gender or age on blood pressure effect of lotrel was demonstrated.

Safety

As summarized in the Medical review, receipt of the higher dose of lotrel (10/20) was associated with an increased rate of discontinuation for adverse events (7.9% vs. 4.8% for the lotrel 5/20). Of the adverse events reported, 'dizziness' and edema were reported more commonly in the lotrel 10/20 group than either the lotrel 5/20 or placebo groups (see Medical Review, page 14). More women than men reported adverse events in the high-dose group, including edema, cough, dizziness and headache.

SUMMARY

The proposed higher dose of lotrel (amlodipine 10/ benazapril 20) had a significant effect to lower blood pressure, although the effect was numerically not statistically superior to the current highest marketed dose of lotrel (amlodipine 5/ benazapril 20). The combination of amlodipine 10 and benazapril 20 mg also seem clearly associated with an increased incidence of relevant adverse events, especially edema and 'dizziness.' As both of these adverse events are monitorable and are seen commonly in products using amlodipine, they do not preclude approval of the new dosage strength, although the effects must be reflected in approved labeling. As there are no approvability issues identified by any of the other review disciplines, this supplement is approvable pending resolution of the labeling issues raised by the chemists and adequate labeling of the observed safety and efficacy of the new dosage form.

RHPM Review of Final Printed Labeling
(container label, physician sample carton and container label, and package insert)
NDA 20-364/SE8-016

Product:	Lotrel (amlodipine/benazepril hydrochloride) Capsules
Sponsor:	Novartis Pharmaceuticals Corporation
Date of FPL submission:	Carton and container labels submitted May 2, 2002 Package insert submitted in hardcopy May 2, 2002, followed by a May 20, 2002 electronic submission
Date of labeling review:	June 13, 2002

Background

This final printed labeling was submitted in response to the Division's April 29, 2002 approvable letter for this supplemental application. The letter stated that the application was approvable, provided the Sponsor submit final printed labeling (package insert and carton and container labels) revised to reflect the changes listed in the letter.

Following the issuance of the approvable letter, the Sponsor submitted to DDMAC their proposed advertising materials for the new dosage strength, including the revised package insert. Upon reviewing the promotional materials and package insert, Dr. Haffer contacted the Division to [redacted]

Dr. Haffer's May 23, 2002 memorandum describes his concerns and provides recommendations for addressing them. In her May 29, 2002 memorandum, Dr. Gordon disagrees with Dr. Haffer's recommendations. In a May 31, 2002 e-mail, Dr. Throckmorton concurs with Dr. Gordon, deciding that changes beyond those already specified for this supplemental application would not be requested.

On May 2, 2002, the Sponsor submitted in paper the final printed carton and container labels and package insert. In response to the Division's request for an electronic final printed package insert, the Sponsor submitted electronically the final printed package insert on May 20, 2002.

Evaluation

I reviewed the May 20, 2002 electronically submitted final printed package insert in its entirety and compared it to the April 17, 2002 electronically submitted proposed package insert ("pi.pdf" version) for this supplemental application. The two package inserts are identical, excepting the change to the **ADVERSE REACTIONS** section specified in the April 29, 2002 approvable letter.

I reviewed the May 2, 2002 submitted final printed container label and physician sample carton and container labels in their entirety. I compared them to the proposed container

label and physician sample carton and container labels included in the original supplemental application. The labels are identical, with the following exceptions:

1. The storage statement was revised as specified in the April 29, 2002 approvable letter.

2. The May 2, 2002 submitted final printed immediate container labels for the 100 capsule bottle and physician sample bottle no longer include the statement "Dosage: See package insert." *(Because the revised storage statement is lengthier than the previous storage statement, there may no longer be room for the dosage statement on these labels.)*

3. The NDC numbers on the physician sample container labels differ.

I discussed the removal of the dosage statement from the container labels with Dr. Srinivasachar. He did not object to these changes. Additionally, I confirmed with Mr. Schlotfeldt of Novartis that the NDC number on the May 2, 2002 submitted physician sample carton label for the new dosage strength is the correct NDC number. He indicated that there was some confusion when the draft labeling was submitted in June of 2001 as to the correct NDC number.

Action

The labeling was revised in accordance with the April 29, 2002 approvable letter. I will draft an approval letter for this supplemental application for Dr. Throckmorton's signature.

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

/s/

Colleen LoCicero
6/18/02 03:04:48 PM
CSO

RHPM Review of Draft Labeling
NDA 20-364/SE8-016

Product:	Lotrel (amlodipine and benazepril HCl) Capsules
Sponsor:	Novartis Pharmaceuticals Corporation
Date of supplemental application:	June 29, 2001
Date of most recent labeling submission:	April 17, 2002
Date of labeling review:	April 24, 2002

Background

This supplemental application provides for a new dosage combination of 10 mg amlodipine and 20 mg benazepril. In addition to the chemistry, manufacturing, and controls information, human pharmacokinetic and bioavailability information, and clinical data that support the application, proposed labeling (package insert and carton and container labels), revised to reflect the addition of the new dosage combination, was included in the original application.

Following a February 5, 2002 teleconference between representatives of Novartis and Dr. Chidambaram, the reviewing chemist, Novartis submitted a revised proposed package insert on February 20, 2002 that reflects Dr. Chidambaram's recommendations. In the February 20, 2002 submission, the Sponsor states that they will revise the draft carton and container labels to conform with the changes in the package insert and provide these to FDA upon request.

Furthermore, in response to a request I related to Mr. Schlotfeldt of Novartis from Dr. Throckmorton, Novartis submitted electronic copies of the proposed package insert on April 15 and 17, 2002. The package inserts included in these submissions were to be identical to the February 20, 2002 submitted package insert. In the cover letter of the April 15, 2002 submitted proposed package insert, the Sponsor notes a change from the February 20, 2002 submitted package insert in the NDC number for the new Lotrel dosage strength in the **HOW SUPPLIED** section.

Upon preliminary review of the April 15 and 17, 2002 submitted proposed package inserts, I noted an additional change in the **HOW SUPPLIED** section (of the April 15, 2002 submitted labeling and the "proposed.doc" and "proposed.pdf" documents in the April 17, 2002 submission) from the February 20, 2002 submitted package insert. Additionally, I noted a difference in the **HOW SUPPLIED** section of the labeling in "pi.pdf" format and that in the "proposed.doc" and "proposed.pdf" formats included in the April 17, 2002 electronic labeling submission. In an April 24, 2002 telephone conversation, Mr. Carl Schlotfeldt of Novartis clarified that the correct proposed text for the package insert is that found in the "pi.pdf" format included in the April 17, 2002 electronic submission. Therefore, I reviewed the April 17, 2002 submitted package insert in "pi.pdf" format for the labeling review.

Labeling review

I reviewed the April 17, 2002 submitted package insert ("pi.pdf" document) in its entirety and compared it to the last approved package insert, final printed package insert submitted for S-008, approved June 16, 1999. I noted the following changes from the June 16, 1999 approved package insert:

1. The heading has been revised to include "10 mg/20 mg" to reflect the addition of the new 10 mg amlodipine/20 mg benazepril combination.

2. The statement "Caution: Federal law prohibits dispensing without prescription" has been replaced with "Rx only."

This change was made to comply with Section 126 of Title I of the Food and Drug Modernization Act of 1997. Section 126 amends section 503(b) of the Federal Food, Drug, and Cosmetic Act to require that the label of prescription products contain the symbol "Rx only" instead of the "Caution: Federal Law prohibits dispensing without prescription" statement. While the regulations do not require that this symbol be included in the package insert, it is permitted.

3. The first sentence in the paragraph that immediately precedes the chemical structure of amlodipine besylate in the **DESCRIPTIONS** section has been revised from the following:

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to the following:

> Amlodipine besylate is a white to pale yellow crystalline powder, slightly soluble in water and sparingly soluble in ethanol.

This change was reported in the August 3, 2001 submitted annual report for the NDA and is presumably acceptable.

4. The first two sentences of the last paragraph of the **DESCRIPTION** section have been revised from the following:

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benazepril hydrochloride.

to the following:

> Lotrel is a combination of amlodipine besylate and benazepril hydrochloride. The capsules are formulated in four different strengths for oral administration with a combination of amlodipine besylate equivalent to 2.5 mg, 5 mg, or 10 mg of amlodipine, with 10 mg or 20 mg of benazepril hydrochloride providing for the following available combinations: 2.5/10 mg, 5/10 mg, 5/20 mg and 10/20 mg.

These changes reflect recommendations made by Dr. Chidambaram in a February 5, 2002 teleconference with the Sponsor. As the Sponsor notes in the correspondence that accompanies the revised labeling, the changes are not identical to those suggested by Dr. Chidambaram. In his February 27, 2002 review of this supplemental application, Dr. Chidambaram notes that although these changes are not exactly as he recommended, they are acceptable.

5. The last sentence of the **DESCRIPTION** section has been revised to include "(potato)" and "(corn)", so that the sentence reads as follows:

> The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil, iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch (potato) glycolate, starch (corn), talc, and titanium dioxide.

This change was reported in the August 3, 2001 submitted annual report for the NDA and is presumably acceptable.

6. The number of patients and studies in the first sentence of the eighth paragraph of the **CLINICAL PHARMACOLOGY/Pharmacodynamics** subsection have been revised from "[redacted]" to "950" and "[redacted]" to "six", respectively, so that the sentence now reads as follows:

> Over 950 patients received Lotrel once daily in six double-blind, placebo-controlled studies.

7. The doses of amlodipine in the ninth paragraph of the **CLINICAL PHARMACOLOGY/Pharmacodynamics** subsection have been revised from "[redacted]" to "2.5-10 mg", so that the sentence now reads as follows:

> Once-daily doses of benazepril/amlodipine using benazepril doses of 10-20 mg and amlodipine doses of 2.5-10 mg decreased seated pressure (systolic/diastolic) 24 hours after dosing by about 10-25/6-13 mmHg.

8. The first sentence of the **PRECAUTIONS/Geriatric Use** subsection has been revised to include the word "over", so that the sentence now reads as follows:

   Of the total number of patients who received Lotrel in U.S. clinical studies of Lotrel, over 19% were 65 or older while about 2% were 75 or older.

9. The number of patients in the first sentence of the **ADVERSE REACTIONS** sentence has been revised from [illegible] to "1850", so that the sentence now reads as follows:

   Lotrel has been evaluated for safety in over 1850 patients with hypertension; over 500 of these patients were treated for at least 6 months, and over 400 were treated for more than 1 year.

10. The first sentence in the second paragraph of the **ADVERSE REACTIONS** section has been revised from the following:

    [illegible]

    to the following:

    In a pooled analysis of 5 placebo-controlled trials involving Lotrel doses up to 5/20, the reported side effects were generally mild and transient, and there was no relationship between side effects and age, sex, race, or duration of therapy.

11. The third paragraph of the **ADVERSE REACTIONS** section has been revised to replace [illegible] with "these", so that the sentence now reads as follows:

    The most common reasons for discontinuation of therapy with Lotrel in these studies were cough and edema.

12. The fourth paragraph of the **ADVERSE REACTIONS** section has been revised to replace [illegible] with "these trials", so that the sentence now reads as follows:

    The side effects considered possibly or probably related to study drug that occurred in these trials in more than 1% of patients treated with Lotrel are shown in the table below.

13. The following sentence has been added to the **ADVERSE REACTIONS** section, immediately following the table on the incidence of certain adverse events by sex:

    In a placebo-controlled study (n=386) which evaluated Lotrel 10/20, the most frequently reported adverse reactions were headache, edema, cough, and

dizziness. The incidence of edema was slightly higher than that observed in studies of lower doses.

14. The last sentence in the paragraph immediately preceding the **ADVERSE REACTIONS/*Fetal/Neonatal Morbidity and Mortality*** subsection has been revised to include "upper respiratory tract infection", so that the sentence now reads as follows:

    These included chest pain, ventricular extrasystole, gout, neuritis, tinnitus, alopecia and upper respiratory tract infection.

15. The amlodipine doses in the second sentence of the **DOSAGE AND ADMINISTRATION** section have been revised from [redacted] to "2.5-10 mg", so that the sentence now reads as follows:

    In clinical trials of amlodipine/benazepril combination therapy using amlodipine dose of 2.5-10 mg and benazepril doses of 10-20 mg, the antihypertensive effects increased with increasing dose of amlodipine in all patient groups.

16. The first paragraph of the **HOW SUPPLIED** section has been revised from the following:

[redacted]

to the following:

    Lotrel is available as capsules containing amlodipine besylate equivalent to 2.5 mg, 5 mg or 10 mg of amlodipine, with 10 mg or 20 mg of benazepril hydrochloride providing for the following available combinations: 2.5/10 mg, 5/10 mg, 5/20 mg and 10/20 mg. All four strengths are packaged with a desiccant in bottles of 100 capsules.

These changes reflect recommendations made by Dr. Chidambaram in his February 5, 2002 teleconference with the Sponsor. As noted in the correspondence that accompanies the revised labeling, the changes are not identical to those suggested by Dr. Chidambaram. In his February 27, 2002 review of this supplemental application, Dr. Chidambaram notes that although the changes are not exactly as he recommended, they are acceptable.

17. In the **HOW SUPPLIED** section, the word [redacted] has been removed from and the corresponding identification number added to the descriptions of each capsule strength under the heading "Capsule Color/Number." Additionally, the following information on the new combination has been added under the appropriate columns of

the table in this section:

10/20 mg
purple (amethyst) with 2 white bands/0364
NDC 0078-0364-05

18. The Storage Statement in the **HOW SUPPLIED** section has been revised from the following:

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to the following:

Storage: Store at 25° C (77° F); excursions permitted to 15°- 30° (59° - 86° F).
[See USP controlled room temperature.]
Protect from moisture. Dispense in tight container (USP).

The revised Storage Statement is identical to that suggested by Dr. Chidambaram in his February 5, 2002 teleconference with the Sponsor, as noted in his February 27, 2002 review of this supplemental application.

Overview of Labeling Recommendations

In his April 16, 2002 secondary review of this supplemental application, Dr. Throckmorton concludes "this supplement is approvable pending resolution of the labeling issues raised by the chemists and adequate labeling of the observed safety and efficacy of the new dosage form."

Chemistry

With respect to the chemistry labeling issues, Dr. Chidambaram finds the February 20, 2002 submitted revised package insert acceptable, as noted in his February 27, 2002 review. He notes the draft carton and container labels included in the original supplemental application and the Sponsor's commitment to revise these carton and container labels to reflect the changes to the package insert. Dr. Chidambaram recommends that the Sponsor submit a final printed package insert and final printed carton and container labels when the supplement is approved.

Clinical

Dr. Gordon did not include written labeling recommendations in her review of this supplemental application, however, she reviewed the proposed labeling and provided her recommendations on the labeling informally to Dr. Throckmorton.

Subsequent to his review of the proposed labeling and Dr. Gordon's recommendations, Dr. Throckmorton recommended the following change to the proposed package insert:

Replacement of the following paragraph that was added to the **ADVERSE REACTIONS** section of the package insert:

with the following:

> In a trial (n=386) comparing placebo, Lotrel 5/20, and Lotrel 10/20, edema and dizziness were most commonly reported in the Lotrel 10/20 group.

None of the remaining review disciplines recommended changes to the proposed labeling.

Action

At Dr. Throckmorton's recommendation, I will draft an approvable letter for this supplemental application for his signature. The approvable letter will specify that final printed labeling (package insert and carton and container labels) revised as follows be submitted for approval of the application:

1. Revision of the carton and container labels for the new dosage strength to reflect the storage statement recommended by Dr. Chidambaram and incorporated in the proposed package insert submitted February 20, 2002 and subsequent labeling submissions.

2. Replacement of the following paragraph that was added to the **ADVERSE REACTIONS** section of the package insert:

with the following:

> In a trial (n=386) comparing placebo, Lotrel 5/20, and Lotrel 10/20, edema and dizziness were most commonly reported in the Lotrel 10/20 group.

Finally, as discussed with Dr. Throckmorton, the letter will not include language pertaining to pediatric studies, as this application (new dosage strength of an existing combination) does not trigger the pediatric rule.

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/s/

Colleen LoCicero
4/29/02 01:30:28 PM
CSO

20 pages redacted from this section of the approval package consisted of draft labeling

RHPM Overview of Approval Package
NDA 20-364/SE8-016

Product:	Lotrel (amlodipine/benazepril HCl) Capsules
Sponsor:	Novartis Pharmaceuticals Corporation

Background

This June 29, 2001 submitted supplemental new drug application proposes a new, higher dosage strength that combines 10 mg. of amlodipine with 20 mg. of benazepril. An approvable letter was issued for this application on April 29, 2002. The letter states that the application is approvable, provided the Sponsor submit final printed labeling (package insert and carton and container labels) revised as described in the letter. On May 2, 2002, the Sponsor submitted final printed labeling for the package insert and carton and container labels in hardcopy. In response to the Division's request for an electronic version of the final printed package insert, the Sponsor submitted the final printed package insert in electronic form on May 20, 2002.

Administrative items

Included in the Action package are copies of the debarment certification, User Fee form, and patent information for this supplemental application. Additionally, the package contains a completed Exclusivity Checklist. No pediatric page is included, as this application does not trigger the pediatric rule.

Labeling

The package contains the Sponsor's original proposed package insert and carton and container labels and the RHPM review of the April 17, 2001 submitted proposed draft package insert.

Following the issuance of the approvable letter, the Sponsor submitted to DDMAC their proposed advertising materials for the new dosage strength, including the revised package insert. Upon reviewing the promotional materials and package insert, Dr. Haffer contacted the Division to _____ Dr. Haffer's May 23, 2002 memorandum describes his concerns and provides recommendations for addressing them. In her May 29, 2002 memorandum, Dr. Gordon disagrees with Dr. Haffer's recommendations. In his May 31, 2002 e-mail, Dr. Throckmorton concurs with Dr. Gordon, deciding that changes beyond those already specified for this supplemental application would not be requested. Dr. Haffer's and Dr. Gordon's memoranda and Dr. Throckmorton's e-mail are included in this package.

Finally, the package contains the Sponsor's May 2, 2002 submitted carton and container labels in hardcopy, a print out of the Sponsor's May 20, 2002 electronically submitted

package insert, and the RHPM review of these labeling submissions. The labeling review concludes that the May 2 and 20, 2002 submitted final printed labeling was revised in accordance with the April 29, 2002 approvable letter.

Division Directors' Memoranda

The package contains Dr. Lipicky's February 28, 2002 memorandum regarding this supplemental application and Dr. Throckmorton's April 16, 2002 memorandum. In his memorandum, Dr. Throckmorton recommends that the application be approved, pending resolution of the labeling issues identified by the chemists and adequate labeling of the observed safety and efficacy of the new dosage strength. Although Dr. Throckmorton's memorandum recommends a deferral of pediatric studies, one was not granted because this application does not trigger the pediatric rule.

Medical Review

The application contains a copy of Dr. Gordon's January 9, 2002 review of this application. Dr. Gordon's review of the April 12, 2002 submitted financial disclosure information for the efficacy study that supports this application is also included in the package.

Statistical Review

Dr. Freidlin's January 15, 2002 review of this supplemental application is included in the package.

Clinical Pharmacology/Biopharmaceutics Review

Dr. Mishina's March 12, 2002 review of this supplemental application is included in the package.

Chemistry Review

In his February 27, 2002 review of this supplemental application, Dr. Chidambaram notes that the Office of Compliance issued an overall acceptable recommendation for the manufacturing sites. He finds acceptable the Sponsor's claim of categorical exclusion from filing an environmental assessment under 21 CFR 25.31 (b). He recommends approval of the application, provided the storage statement in the package insert and on the carton and container labels is revised to reflect the changes to which the Sponsor agreed.

On June 14, 2002, Dr. Srinivasachar confirmed that we did not request that the methods be validated for this application, as the methods are similar to the methods currently used to manufacture the approved, marketed strengths of this combination product.

Action

As the submitted final printed labeling is in accordance with the April 29,2002 submitted approvable letter, I will draft an approval letter for Dr. Throckmorton's signature.

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/s/

Colleen LoCicero
6/18/02 03:12:16 PM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 20-364	Efficacy Supplement Type SE-8	Supplement Number 016
Drug: Lotrel (amlodipine/benazepril HCl) Capsules	Applicant: Novartis Pharmaceuticals Corporation	
RPM: Colleen LoCicero	HFD-110	Phone # 4-5332
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	Primary: 5/2/02 (approvable letter issued 4/29/02) Secondary: 7/2/02
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X-June 14, 2002
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE-4/29/02
• Status of advertising (approvals only)	(X) Materials submitted 5/6/02 ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X (DDMAC memo, MO memo, DD memo, RHPM review)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	See Chemistry review & RHPM review of FPL.
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-sNDA meeting (indicate date)	X-August 22, 2000
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Dr. Lipicky review-2/28/02 Dr. Throckmorton review-4/16/02
❖ Clinical review(s) *(indicate date for each review)*	Dr. Gordon review-1/9/02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A (this application does not trigger the pediatric rule)
❖ Statistical review(s) *(indicate date for each review)*	Dr. Freidlin-1/15/02
❖ Biopharmaceutical review(s) *(indicate date for each review)*	Dr. Mishina-3/12/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	None requested
• Bioequivalence studies	None requested
❖ CMC review(s) *(indicate date for each review)*	Dr. Chidambaram-2/27/02
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Included in Dr. Chidambaram's 2/27/02 review (p. 5)
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: 8/27/01 **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed **( )** Requested **(X)** Not requested (See RHPM overview.)
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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

/s/

Colleen LoCicero
6/18/02 03:17:47 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Novartis Pharmaceuticals Corp.
59 Route 10
East Hanover, New Jersey 07936

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 781-6869 - Robert Kowalski, PharmD.

3. PRODUCT NAME

Lotrel

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

4151

6. LICENSE NUMBER / NDA NUMBER

NDA 20-364

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

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

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Robert Kowalski, PharmD.	Director, Global Head DRA	5/30/01

FORM FDA 3397 (5/98)