

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020261/S018/S022

ENVIRONMENTAL ASSESSMENT AND/OR FONSI



Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

EAWAIVER.DOC 23-Nov-98 (5:40PM)

ENVIRONMENTAL ASSESSMENT

As set forth in 21 CFR Part 25.31(a) [Federal Register, Volume 62, Number 145, dated July, 29, 1997], action on an NDA is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action does not increase the use of the active moiety.

Novartis Pharmaceuticals Corporation certifies that this submission to revise the WARNINGS liver function monitoring requirements and to add triglycerides information to the CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE sections for Lescol Capsules qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(a) as this action will not increase the use of the active moiety, fluvastatin sodium.

Further, Novartis Pharmaceuticals Corporation states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020261/S018/S022

PHARMACOLOGY REVIEW(S)

NDA 20-261/S018

Review Completed: October 2, 1998

Sponsor: Novartis Pharmaceuticals Corp; 59 Route 10; East Hanover, NJ 07936

PHARMACOLOGY REVIEW OF NDA SUPPLEMENT
Supplement to NDA 20-261 #018

DRUG: Lescol® (fluvastatin sodium) Capsules

CATEGORY: Lescol® efficacy supplement. Addition of triglyceride information in the indications and usage section.

INDICATION: This supplement provides for use in combination with metformin in the lowering of blood glucose as an adjunct to diet.

PHARMACOLOGY COMMENTS: There were no preclinical data submitted under supplement #018. Therefore, no pharmacology review is necessary for this supplement. There were no labeling changes made to the previously approved preclinical sections of the label.

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Simoneau
Recommendation code: AP

/S/

Ronald W. Steigerwalt, Ph.D.

10/2/98

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020261/S018/S022

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

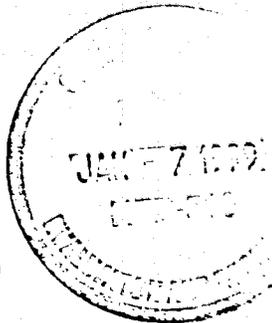
 **NOVARTIS**

APPROVED

MAR - 6 1999

January 6, 1999

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-04
Center for Drug Evaluation
and Research
5600 Fishers Lane
Rockville, Maryland 20857



NDA No. 20-261
LESCOL® (fluvastatin
sodium) Capsules

DRAFT Final Printed Labeling

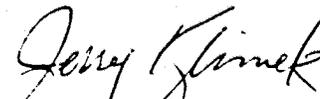
Dear Dr. Sobel:

Reference is made to our supplemental NDA submitted on July 21, 1998 for Lescol® (fluvastatin sodium) Capsules NDA No. 20-261 and to correspondence with Ms. Margaret Simoneau on January 6, 1999 with regard to a minor revision to the CLINICAL PHARMACOLOGY, Clinical Studies section where the word "combined" was removed from the first paragraph under this section.

We are providing with this correspondence draft final printed labeling with this correction as requested by Ms. Simoneau. Please note that the revised narrative is underlined.

If there are any questions or concerns with this submission or if you need further assistance please contact me at 973-781-8145.

Sincerely,


Jerry Klimek
Associate Director
Drug Regulatory Affairs

Attachments in duplicate
Desk Copy: Ms. Margaret Simoneau
 Dr. David Orloff

 **NOVARTIS**

DUPLICATE

COPY 2

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

Tel 973 781 7500
Fax 973 781 6325

December 1, 1998

NDA SUPP AMEND

SEI-018 BC

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-04
Center for Drug Evaluation
and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-261

**LESCOL® (fluvastatin
sodium) Capsules**

FDA Request for Information

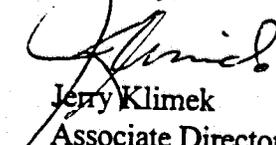
Dear Dr. Sobel:

Reference is made to our supplemental NDA submitted on July 21, 1998 for Lescol® (fluvastatin sodium) Capsules NDA No. 20-261. Reference is also made to recent telephone conversations (November 17 and 23, 1998) with Dr. David Orloff and Ms. Margaret Simoneau with regard to the supplemental NDA for Lescol (fluvastatin sodium) Capsules where proposed labeling was submitted for revisions to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, and WARNINGS sections for triglyceride and liver function test monitoring information.

We are providing with this correspondence an eleven page data listing titled: **Liver Function Test/ All Placebo-Controlled Studies/ Listing of Subjects with SGOT or SGPT > 3xULN** which was referenced in our telephone conversation with Dr. David Orloff on November 17, 1998. We are also providing a copy of the Environmental Assessment Waiver for this submission as requested by Ms. Simoneau in a telephone conversation on November 23, 1998.

If there are any questions or concerns with this submission or if you need further assistance please contact me at 973-781-8145.

Sincerely,


Jerry Klimek
Associate Director
Drug Regulatory Affairs

Attachments in duplicate

Desk Copy: Ms. Margaret Simoneau (Environmental Assessment Waiver)
Dr. David Orloff (Liver Function Test Listing)



January 4, 1998

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-04
Center for Drug Evaluation
and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-261
LESCOL® (fluvastatin
sodium) Capsules

DRAFT Final Printed Labeling

Dear Dr. Sobel:

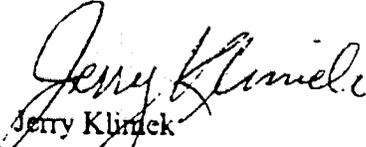
Reference is made to our supplemental NDA submitted on July 21, 1998 for Lescol® (fluvastatin sodium) Capsules NDA No. 20-261 and to correspondence with Dr. David Orloff on December 30, 1998 with regard to revisions to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE and WARNINGS sections for triglyceride and liver function test monitoring information.

We are providing with this correspondence draft final printed labeling as requested by Dr. Orloff. Please note that the revised narrative is underlined.

If there are any questions or concerns with this submission or if you need further assistance please contact me at 973-781-8145.

BEST POSSIBLE COPY

Sincerely,


Jerry Klimick
Associate Director
Drug Regulatory Affairs

Attachments in duplicate
Desk Copy: Ms. Margaret Simoneau
Dr. David Orloff

NOVARTIS

July 21, 1998



Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-04
Center for Drug Evaluation
and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-261
LESCOL® (fluvastatin
sodium) Capsules

Supplemental NDA

Dear Dr. Sobel:

Reference is made to our approved Lescol® (fluvastatin sodium) Capsule New Drug Application 20-261 dated March 31, 1992 and to the approved Supplemental New Drug Applications S-006 (80 mg [40 mg bid]) dated March 23, 1995 and S012 (Lipoprotein and Coronary Atherosclerosis Study, LCAS) dated October 1, 1996. Reference is also made to telephone conversations with Dr. David Orloff on September 25, 1997 and Ms. Margaret Simoneau on May 13, 1998 with regard to a Supplemental New Drug Application in support of revisions to our current package insert for liver function test monitoring and triglycerides.

We are providing with this correspondence proposed labeling changes for Lescol® (fluvastatin sodium) Capsules with regard to revising the **WARNINGS** liver function test monitoring requirements and adding to the **CLINICAL PHARMACOLOGY** and **INDICATIONS AND USAGE** sections triglyceride information as supported by pooled analyses of previously submitted double-blind, placebo controlled trials (please refer to attached Liver Function Test Monitoring and Primary Mixed Hyperlipidemia Reports Text Table 1 for listing of controlled trials). We are cross referencing the listed double-blind, placebo controlled study reports from the original Lescol® New Drug Application (dated March 31, 1992) and from two Lescol® Supplemental New Drug Applications (dated March 23, 1995 and October 1, 1996). We are also including with this submission annotated labeling, a Liver Function Test Monitoring Report, a Primary Mixed Hyperlipidemia Report, and the pooled data base of the double-blind, placebo controlled trials on computer diskettes with hard copies of Proc Contents.

This submission contains a report entitled "Liver Function Test (LFT) Monitoring" which discusses the results of a pooled analysis of all Lescol® (fluvastatin sodium) placebo-controlled studies of at least 6 weeks and up to 130 weeks. The results indicate that all patients with persistent (two consecutive occasions) transaminase elevations >3 times the upper limit of normal will be effectively monitored at baseline and eight weeks. After 12 weeks there is no difference in liver function test abnormalities >3 times the upper limit of normal for either the fluvastatin or placebo treated patients. Therefore we are

Solomon Sobel, M.D.

-2-

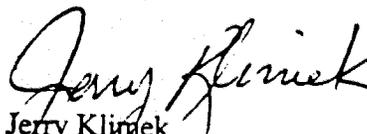
proposing changes to the WARNINGS section of the labeling to recommend that liver function tests only be performed before initiation of therapy and at 8 weeks following initiation of treatment or elevation in dose.

The submission also contains a report entitled "Primary Mixed Hyperlipidemia" which discusses the results of a pooled analysis of all Lescol® (fluvastatin sodium) placebo controlled studies in patients with primary combined (mixed) hyperlipidemia (Type IIb) defined as baseline triglyceride levels ≥ 200 mg/dL. The results indicate consistent and significant decreases in Total-C, LDL-C, TG and Apo B and modest increases in HDL-C. Therefore we are proposing changes to the CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE sections to include triglyceride and Apo B for primary hypercholesterolemia and mixed hyperlipidemia (Frederickson Type IIa and IIb).

The supplemental User Fee number for this submission is #3519.

If there are any questions or concerns with this submission or if you need further assistance please contact me at 973-781-8145.

Sincerely,


Jerry Klimek
Associate Director
Drug Regulatory Affairs

Attachments in duplicate

Desk Copies: David Orloff, M.D., Ms. Margaret Simoneau, Solomon Sobel, M.D.

DRUG REGISTRATION & REGULATORY AFFAIRS

TEL 201 503 7500
FAX 201 503 6325

October 11, 1994

Solomon Sobel, MD
Director
Division of Metabolism and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-04
Center for Drug Evaluation
and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 20-261
LESCOL® (fluvastatin
sodium) Capsules

NEW DRUG APPLICATION -
SUPPLEMENTAL
APPLICATION

Dear Dr. Sobel:

Please refer to the subject New Drug Application which was submitted in original form on March 31, 1992.

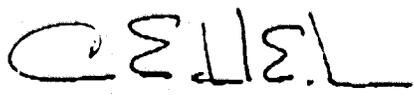
The purpose of the present submission is to supplement Section 13 (patent information on any patent which claims the drug) of the Application with the following information:

United States Patent 5,354,772 issued on October 11, 1994, and will expire on October 11, 2011.

This patent covers **LESCOL® (fluvastatin sodium)** and its use for inhibiting cholesterol biosynthesis and the treatment of atherosclerosis.

If you have any questions or comments, please contact me at (201)503-8601.

Sincerely,



C. Edward Eden, Ph.D.
Associate Director
Management and Administration

CEE/rva
Submitted in triplicate

EXCLUSIVITY SUMMARY FOR NDA # 20-261 SUPPL # 18

Trade Name LESICOL

Generic Name FLUVASTATIN Sodium

Applicant Name NOVARTIS

HFD # 510

Approval Date If Known _____

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 question about the submission.

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

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

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

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 / / 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 / /

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

3 per 21 CFR 314.108 (b)(4)

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

no

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 / /

If yes, NDA # _____

Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 / /

APPEARS THIS WAY
ON ORIGINAL

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

NDA# 20-261 lescol
NDA# _____
NDA# _____

2. Combination product. *NA*

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 / / NO / /

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

NDA# _____
NDA# _____
NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. 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 / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 / / 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 8:

(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 / /

(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 / /

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:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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.

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 # _____ YES /___/ ! NO /___/ Explain: _____
 !
 !
 !

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 / /

If yes, explain: _____

Signature
Title: _____

/S/

Date

January 19, 1999

Signature of Office/
Division Director

/S/

Date

3/8/99

cc: Original NDA

Division File

HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 20-261/S-018

Supplement # 18

Circle one SE1 SE2 SE3 SE4 SE5 SE6

Trade and generic names/dosage form: Lescol (Fluvastatin) Action: AP AE NA

Applicant Novartis Therapeutic Class _____

Indication(s) previously approved hypercholesterolemia and mixed dyslipidemia; atherosclerosis

Pediatric information in labeling of approved indication(s) is adequate inadequate

Proposed indication in this application _____

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1month) Infants (1month-2yrs) Children (2-12yrs) Adolescents(12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
 - c. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing.
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, attach memo describing status of discussions.
 - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Team Leader (e.g., medical review, medical officer, team leader)

IS/ Tim, Leader 1-19-99
Signature of Preparer and Title Date

Orig NDA/BLA # _____
HF _____/Div File
NDA/BLA Action Package
HFD-006/ KRoberts

Lescol[®] (fluvastatin sodium) Capsules
New Drug Application

NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

NOVARTIS PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

7/21/98
July 21, 1998

Jerry Klimek
Jerry Klimek
Associate Director
Drug Regulatory Affairs