

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-192

ADMINISTRATIVE DOCUMENTS

13/14 Patent Information/Patent Certification

Lescol XL (fluvastatin sodium) Extended Release Tablets NDA No. 21-192

Patent Numbers: U.S. 5,354,772 and
U.S. 5,356,896

Patent Expiration Dates: October 11, 2011 and
December 12, 2011

Type of Patent: Composition and
Formulation

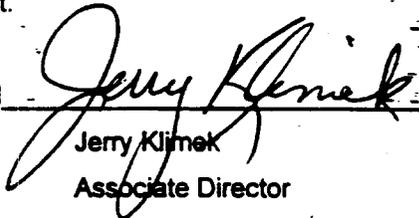
Name of Patent Owner: Novartis Pharmaceuticals Corporation

Indication: Hypercholesterolemia (heterozygous familial and non
familial) and Mixed Dyslipidemia

Strength: 80 mg

The undersigned declares that the above stated United States Patent Numbers cover the composition, formulation and/or method of use of Lescol XL (fluvastatin sodium) Extended Release Tablets. This product is the subject of this application for which approval is being sought.

Signed


Jerry Klimmek

Associate Director
Drug Regulatory Affairs

Date

Dec 8, 1999

Exclusivity Checklist

NDA: 21-192				
Trade Name: Lescol XL				
Generic Name: fluvastatin sodium extended release tablets				
Applicant Name: Novartis				
Division: HFD-510				
Project Manager: William C. Koch, R.Ph.				
Approval Date:				
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	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
b. Is it an effectiveness supplement?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)				
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	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
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.				
Explanation:				
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:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (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.	Yes	X	No	
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	X	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product	Lescol			
NDA #	20-261			
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	X
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 <u>any one</u> 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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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.				

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	
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If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.

Basis for conclusion:

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	X	No	
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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	X
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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	
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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 #:	XUO-F302
Investigation #2, Study #:	XUO-F351
Investigation #3, Study #:	XUO-F353

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	X
Investigation #3	Yes		No	X

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

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

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	X
Investigation #3	Yes	No	X
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number			
Investigation #3 -- NDA Number			
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 #1	XUO-F302		
Investigation #2	XUO-F351		
Investigation #3	XUO-F353		
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	Yes	X	No
IND#: _____			
Explain:			
Investigation #2	Yes	X	No
IND#: _____			
Explain:			
Investigation #3	Yes	X	No
IND#: _____			
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	No	
IND#: _____			
Explain:			
Investigation #2	Yes	No	
IND#: _____			
Explain:			
Investigation #3	Yes	No	
IND#: _____			
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:				

LSI

09/27/00

Signature of PM

Date:

LSI

10.6.00

Signature of Division

Date:

cc:

- Original NDA
- HFD-510/Division File
- HFD-93/Mary Ann Holovac
- HFD-104/TCrescenzi

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: 021192 **Trade Name:** LESCOL XL (FLUVASTATIN SODIUM) 80MG ER T

Supplement Number: 000 **Generic Name:** FLUVA STATIN SODIUM

Supplement Type: N **Dosage Form:**

Regulatory Action: AP **COMIS Indication:**

Action Date: 10/6/00

Indication # 1

A new extended release dosage form, as an adjunct to diet to increase HDL-C in patients with primary hypercholesterolemia and mixed lipidemia (Frederickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures has not been adequate.

Label Adequacy: Inadequate for ALL pediatric age groups

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): Ages 0 - 9 yrs waived (May 24, 2000)

Lower Range	Upper Range	Status	Date
10 years	16 years	Deferred	10/6/00

Comments:

Indication # 2

A new extended release dosage form, as an adjunct to diet to reduce total cholesterol (Total-C), LDL-C, TG, and Apo-B levels in patients with primary hypercholesterolemia and mixed lipidemia (Frederickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures has not been adequate.

Label Adequacy: Inadequate for ALL pediatric age groups

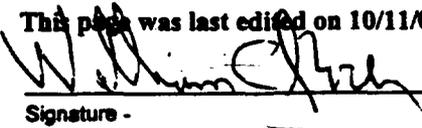
Formulation Needed: NO NEW FORMULATION is needed

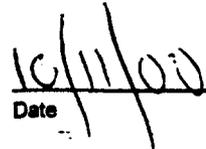
Comments (if any): Ages 0 - 9 yrs waived (May 24, 2000)

Lower Range	Upper Range	Status	Date
10 years	16 years	Deferred	10/6/00

Comments:

This page was last edited on 10/11/00


Signature -


Date

LESCOL XL[®] (fluvastatin sodium) Extended Release Tablets
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.

Dec. 8, 1999
Date

Jerry Klimek
Jerry Klimek
Associate Director
Drug Regulatory Affairs

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached spreadsheets	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Leonard M. Gonasun, Ph.D.	TITLE Director, Clinical Research
FIRM/ORGANIZATION Novartis Pharmaceuticals Corporation	
SIGNATURE 	DATE 12/5/99

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right.

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

**DISCLOSURE: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

The following information concerning See attached spreadsheets, who participated as a clinical investigator in the submitted study _____

See attached spreadsheets, is submitted in accordance with 21 CFR part _____

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

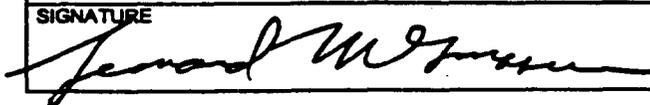
any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

any proprietary interest in the product tested in the covered study held by the clinical investigator;

any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Leonard M. Gonasun, Ph.D.	Director, Clinical Research
FIRM/ORGANIZATION	
Novartis Pharmaceuticals Corporation	
SIGNATURE	DATE
	12/5/99

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Item 19 – Financial Disclosure

Overview:

- **Process used to collect information retrospectively**
 - Letters were sent out to all investigators requesting financial disclosure information
 - A follow up letter was sent to investigators if no reply was received after four weeks and an additional letter four weeks later if necessary
 - At study close out and/or as part of retrospective collection the investigators were told to update Novartis for 1 year from LPLV (last patient last visit) at their site if any change
 - retrospective collection of financial disclosure information (for studies on going 2/2/99)

- **Methods used to minimize bias**
 - independent data monitoring via Novartis or CRO
 - multiple investigators used in the studies
 - double-blind active controlled trials used

- **Description of Spreadsheets**
 - shows principal investigator, subinvestigators, children & spouses (if applicable)
 - shows forms received
 - shows whether there was something to disclose
 - shows if investigator refused to reply

- **Summary of Findings**

- Only two investigators had financial information to disclose in Lescol study No. Xuo-F351-E-00 (at center 26). The principal investigator, W. Brown and sub-investigator, — reported that they had received grant money from Novartis.

**Lescol® (fluvastatin sodium) Capsules
Lescol® XL (fluvastatin sodium) Extended-release Tablets**

NDA 21-192

US Package Insert

Revised Draft Labeling

September 28, 2000

**Property of Novartis Pharmaceuticals
Confidential**

**May not be used, divulged, published or otherwise disclosed
without the consent of Novartis Pharmaceuticals**

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

Lescol[®] (fluvastatin sodium) Capsules
Lescol XL[®] (fluvastatin sodium) Extended Release Tablets

NDA 21-192

US Package Insert

**Division of Metabolic and
Endocrine Drug Products**
Proposed revisions

September 14, 2000

Property of Novartis Pharmaceuticals
Confidential
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis Pharmaceuticals

GENERAL DIVISION NOTES:

Division additions will be in all caps and bracketed {} for easy reference.

Division deletions will be single strikethrough

All tables, graphs and figures should be numbered consecutively throughout the body of the package insert.

GENERAL COMMENTS FROM THE BIOPHARMACEUTICS TEAM

Study W251-Relative bioavailability of the fluvastatin 80 MR tablets under 2.5 h post-prandial and fed conditions:

Labeling should indicate that the _____ formulation resulted in a slower absorption and much lower systemic availability and peak concentrations under fed and 2.5 h post prandial conditions as compared to 80 mg of the marketed immediate release capsule (2 x 40 mg) administered under fasted conditions.

Labeling should indicate that systemic availability and Cmax are greatly reduced for the to be marketed _____ tablet under both fed and 2.5 post-prandial conditions (AHA meals used) as compared to the immediate release capsule given under fasting conditions.

Study W351-Effect of food on the bioavailability of fluvastatin MR 80 mg tablet:

In the submission the sponsor states that fluvastatin concentrations increased gradually with concentrations persisting even at 24 hours, and that this supports the lack of dose dumping of the _____ tablet. Looking at the individual subject concentration vs time profiles, it can be seen that in general, concentrations do not increase gradually, but increase rather abruptly. This is especially true for the fed treatment. However, it is difficult to access whether this is due to rapid release, concentration dependent nonlinearity, or a combination of both. As for the persistence of fluvastatin at 24 hrs in many subjects, it is unclear why this is happening, and it is not consistent with the reported terminal half live of the drug. The sponsor should address the persistent fluvastatin concentrations at 24 hours. _____ wording in the labeling should not be allowed at the present time.

The high degree of variability in the pharmacokinetics of the _____ tablet under fasting conditions, and the increased variability under fed conditions should be noted in the labeling.

The large increase in systemic availability (AUC and Cmax) for fluvastatin from the _____ tablet after a high fat meal as compared to fasting should be noted in the labeling.

The gender effect (increased systemic availability for females) should be noted in the labeling.

The large intersubject variability and much lower intrasubject variability in the pharmacokinetic measures for the _____ tablet should be noted in the labeling.

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

WITHHOLD 4 PAGE (S)

**Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 31, 2000

NDA NUMBER: 21-192

NAME OF DRUG: Lescol XL (Fluvastatin Sodium Extended-release Tablets) 80 mg

NDA HOLDER: Novartis Pharmaceuticals Corp.

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for assessment of the tradename Lescol XL, regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

The proprietary name Lescol was approved for Fluvastatin Sodium Capsules on December 31, 1993 under NDA 20-261. The sponsor, Novartis, has submitted a new NDA for an extended-release formulation of Fluvastatin Sodium and have proposed the proprietary name Lescol XL for this product. Fluvastatin sodium is a competitive inhibitor of HMG-CoA reductase, a precursor of sterols, including cholesterol. Lescol XL is indicated as an adjunct to diet to reduce elevated total cholesterol, LDL-C, TG and Apo B levels, and to increase HDL-C in patients with primary hyper-cholesterolemia and mixed dyslipidemia whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate. Lescol XL is also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels. The recommended starting dose for the majority of patients is 40 mg or 80 mg depending on individual baseline LDL-C levels and associated risk factors. Patients who require only a mild reduction of LDL-C may be started at 20 mg. The recommended dosing range is 40 mg to 80 mg/day as a single dose in the evening. Lescol XL will be available as an 80 mg tablet in bottles of 30 and 100.

II. RISK ASSESSMENT

The standard OPDRA proprietary name review was not completed for this consult because Lescol, has been utilized in the marketplace since 1993. An Expert Panel discussion was conducted to address the review Divisions concern that the modifier "XL" will be confused as a Roman numeral. In addition, the Adverse Event Reporting System (AERS) and Drug Quality Reporting System (DQRS) databases were searched to determine if there is any current confusion with the use of the proprietary name "Lescol".

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name Lescol XL. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. In addition, the panel discussed the concerns regarding the use of the modifier "XL". This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

The modifier "XL" is widely recognized and is an accepted abbreviation for "extended-release". The Agency has approved the following proprietary names in which XL is utilized as a modifier: Procardia XL, Ditropan XL, Toprol XL, Glucotrol XL, Lodine XL and Biaxin XL and Minipress XL. To date, Procardia XL is the only drug in which there was confusion associated with the modifier. In this case "XL" was misinterpreted for "SL", meaning sublingual. This error resulted because several practitioners would puncture the capsule and administer the contents under the tongue.

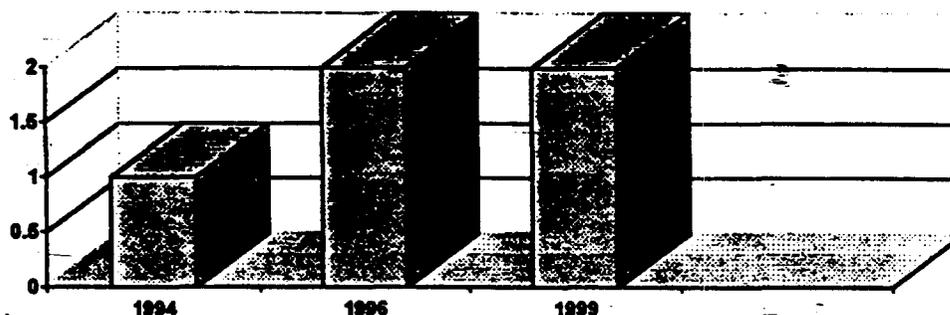
In addition, DDMAC did not have any concerns about the name with regard to promotional claims.

B. AERS and DQRS searches

OPDRA conducted a search in the AERS database for all post-marketing safety reports of medication errors associated with the proprietary name Lescol, using the Meddra Preferred Term "Drug Maladministration". The DQRS database was also searched for similar reports with Lescol. The results of these searches are summarized briefly in Table 1.

TABLE 1

INTENDED Product	DISPENSED Product	Outcome	Cause	AERS/DQRS #
Incorrect Drug (n=5)				
Lasix 40 mg unit-dose tablet	Lescol 40 mg unit-dose capsule	Hospitalization Prolonged	Dispensing error	3327503-5-00-01
Lesco, 20 mg unit-dose capsule	Lipitor 10 mg unit-dose tablet	Not Administered to Patient	Dispensing error	3363250-1-00-01
Pravachol 40 mg tablet	Lescol 40 mg capsule	Not Administered to Patient	Dispensing error	U 080529
Levoxyl tablet	Lescol capsule	Unknown	Dispensing error	U 042047
Levatol 20 mg tablet	Lescol 20 mg capsule	Unknown	Dispensing error	M 115905



In *five* (5) cases, an incorrect drug was dispensed, *one* of which resulted in an additional day of hospitalization. Two of the five errors describe no patient outcome.

The dispensing errors occurred with products that share an overlapping strength. Two of the errors were attributed to similar unit-dose packaging configurations, which can be addressed with labeling revisions such as differentiation of the product strengths with the use of boxing, contrasting colors or some other means. The problem concerning name confusion is not as easily addressed. Since approval, these errors occurred randomly and share no apparent pattern of cause, other than overlapping strengths. OPDRA will continue to monitor post-marketing medication errors in association with the proprietary name. However, based on these reports, OPDRA would not recommend any interventions with regard to the proprietary name at this time.

- C. After review of the package insert labeling, OPDRA is concerned that this product may not actually be an extended-release formulation and therefore, the use of the modifier "XL" would be misleading. The insert states that following oral administration of the immediate release capsule, peak concentrations are reached in less than 1 hour and following administration as the extended-release tablet, peak concentrations are reached in approximately 3 hours. The dosing interval is once daily for both the immediate release capsule and extended-release tablet. There used to be a requirement of a two-fold reduction in the dosing interval for a drug to be considered extended-release. For example: Procardia reaches peak plasma concentrations within 30 minutes and is dosed three times daily, while Procardia XL reaches peak concentrations within 6 hours and is dosed once daily. Lodine reaches peak plasma concentrations within 1 to 2 hours and is dosed every 6 to 8 hours, while Lodine XL reaches peak plasma concentration within 6 hours and is dosed once daily.

Glucotrol and Glucotrol XL are similar to Lescol and Lescol XL in that they are both dosed daily however the pharmacokinetics are different. Glucotrol reaches peak plasma concentration within one to 3 hours, while Glucotrol XL reaches peak plasma concentration within six to twelve hours.

OPDRA contacted the review chemist for clarification on the issue. The chemist stated that the sponsor proposed a formulation with ~~in-vitro~~ *in-vitro* release and is therefore considered the proposed formulation extended-release. If the 20 mg and 40 mg capsules cannot pass this *in-vitro* release test as well, then OPDRA has no objections to the use of the modifier "XL".

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

A. CONTAINER (7s, 30s, 100s)

1. The statement "per tablet" appears more prominent than "fluvastatin" and its placement on the label is distracting. We recommend deleting it from the label or relocating it to appear in conjunction with "fluvastatin".
2. The established name must be revised ~~in order to have the~~ in order to have the proprietary name Lescol XL. Revise to read as follows:

Lescol XL
(Fluvastatin Sodium)

B. INSERT

DOSAGE AND ADMINISTRATION

In reviewing the second paragraph of this section we offer the following comments and observations:

1. The recommended dosing range has been increased from 20 mg to 80 mg/day to ~~80 mg to~~ 80 mg/day. This has eliminated the 20 mg dose within this recommendation.

The proposed:

~~is~~ is misleading since an 80 mg dose of the immediate release capsule must be administered as 40 mg BID. This should be revised accordingly.

IV. RECOMMENDATIONS

- A. OPDRA has reservations to recommending to the use of the proprietary name "Lescol XL". We are concerned this product may not actually be an extended-release formulation and therefore the use of the modifier "XL" would be misleading.
- B. We have made recommendations for labeling revisions to minimize potential errors with the use of this product.

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph, Project Manager at 301-827-3161.

LS 9-28-00
Carol Holquist, R.Ph. U
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

LS 9/29/2000
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

REQUEST FOR CONSULTATION

Division/Office) HFD-400 Attn: Sammie Beam FROM: HFD-510, Metabolic and Endocrine Drug Products
15B03

DATE July 21, 2000 IND NO. NDA NO. 21-192 TYPE OF DOCUMENT New Drug Application DATE OF DOCUMENT December 8, 1999

NAME OF DRUG Levclo XL (fluvastatin sodium extended release tablets) PRIORITY Standard CLASSIFICATION OF DRUG Not Determined DESIRED COMPLETION DATE September 15, 2000

NAME OF FIRM Novartis Pharmaceuticals Corp.

REASON FOR REQUEST

- I. GENERAL**
- NEW PROTOCOL
 - PRE-NDA MEETING
 - RESPONSE TO DEFICIENCY LETTER
 - PROGRESS REPORT
 - END OF PHASE II MEETING
 - FINAL PRINTED LABELING
 - NEW CORRESPONDENCE
 - RESUBMISSION
 - LABELING REVISION
 - DRUG ADVERTISING
 - SAFETY/EFFICACY
 - ORIGINAL NEW CORRESPONDENCE
 - ADVERSE REACTION REPORT
 - PAPER NDA
 - FORMULATIVE REVIEW
 - MANUFACTURING CHANGE/ADDITION
 - CONTROL SUPPLEMENT
 - OTHER (SPECIFY BELOW)
 - MEETING PLANNED BY
 - Trade Name Review

- II. BIOMETRICS**
- | | |
|--|---|
| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW
<input type="checkbox"/> END OF PHASE II MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER |

- III. BIOPHARMACEUTICS**
- DISSOLUTION
 - DEFICIENCY LETTER RESPONSE
 - AVAILABILITY STUDIES
 - PROTOCOL-BIOPHARMACEUTICS
 - PHASE IV STUDIES
 - IN-VIVO WAIVER REQUEST

- IV. DRUG EXPERIENCE**
- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 - REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 - DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 - SUMMARY OF ADVERSE EXPERIENCE
 - CASE REPORTS OF SPECIFIC REACTIONS (List below)
 - POISON RISK ANALYSIS
 - COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- V. SCIENTIFIC INVESTIGATIONS**
- CLINICAL
 - PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Division concerned re: possible confusion of "XL" with roman numerals. Please review the attached Draft label (mock-up of container and carton labeling requested) of NDA. Sharon Kelly, Ph.D. is the reviewing chemist, (301) 827-6394. William C. Koch, R.Ph., Regulatory Project Manager, (301) 827-6412.

SIGNATURE OF RECEIVER *KS* METHOD OF DELIVERY (Check one) **HAND**
SIG OF DELIVERER *KS* 07/31/00

Consult.088

Team Leader Concurrence: *KS* 7-24-00
David G. Orloff, M.D. Date

ORIGINAL NDA 21-192
HFD-510 DIV. FILES

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

FDA CDER EES-
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21192/000
Stamp: 09-DEC-1999 Regulatory Due: 09-OCT-2000
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080

Priority: 3S
Action Goal:
Brand Name: LESCOL XL (FLUVASTATIN SODIUM)
80MG ER T
Established Name:
Generic Name: FLUVASTATIN SODIUM
Dosage Form: EXT (EXTENDED-RELEASE TABLET)
Strength: 80 MG

Org Code: 510
District Goal: 10-AUG-2000

FDA Contacts: S. KELLY (HFD-510) 301-827-6394 , Review Chemist
S. MOORE (HFD-510) 301-827-6430 , Team Leader

Overall Recommendation:

ACCEPTABLE on 05-OCT-2000 by S. ADAMS (HFD-320) 301-594-0095

Establishment: 2416082
NOVARTIS PHARMA INC (CIBA)
OLD MILL RD
SUFFERN, NY 10901

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-APR-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE STABILITY
TESTER

Establishment: 9692043
NOVARTIS PHARMA INC (CIBA)
SCHAFFHAUSERSTRASSE
CH-4332 STEIN, , SZ

DMF No:
AADA No: 020261

Profile: TTR OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-JUN-2000
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE
MANUFACTURER

Establishment: 2210396
NOVARTIS PHARMA INC (SANDOZ)
59 RT 10
EAST HANOVER, NJ 079361080

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-SEP-2000
Decision: ACCEPTABLE

Responsibilities: FINISHED DOSAGE STABILITY
TESTER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Reason: **DISTRICT RECOMMENDATION**

Establishment: **9614433**
NOVARTIS PHARMANALYTICA SA
LOCARNO, , SZ

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **05-OCT-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE STABILITY
TESTER**

Establishment:

DMF No:
AADA No:

Profile: **TTR** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-APR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

NDA 21-192
Lescol XL 80 mg
10/05/00

NDA# 21-192

Product: Lescol (fluvastatin sodium) XL 80 mg extended release tablets

Sponsor: Novartis

Category: Lipid altering

Proposed:

Initial marketing of 80 mg extended release (ER) dosage form, combined label with Lescol capsules (NDA 20-261), change in *Indications* to add "and to increase HDL-C" to indication to treat Fredrickson Types IIa and IIb, removal of previously recommended 40 mg BID optional dose in lieu of 80 mg ER once daily, change in the recommended starting dose of fluvastatin, and other labeling changes reflecting additional lipid altering and safety information derived from the 80 mg ER development program

Date of submission: December 8, 1999

Division Director's memorandum on pending NDA

Introduction

This NDA proposes initial marketing of a new, 80 mg extended-release (ER) dosage form of Lescol (fluvastatin sodium), an approved HMG-CoA reductase inhibitor (statin) under NDA 20-261. The original Lescol NDA was approved December 31, 1993 at doses of 20 or 40 mg once daily. NDA 20-261/S-006, approved March 20, 1996, allowed for the use of 80 mg daily given as 40 mg BID. In addition, supplemental NDAs have been approved supporting indications to lower TG and apo B in patients with Fredrickson types IIa and IIb and supporting an indication to slow the progression of coronary atherosclerosis in patients with coronary artery disease.

This application also proposes to add to the Indications and Usage section of the label the phrase "and to increase HDL-C," reflecting this expected effect of fluvastatin in patients with primary hypercholesterolemia and mixed dyslipidemia. A supplement supporting this change to the labeling for Lescol (NDA 20-261) is pending in the Division.

Of note, also, the sponsor proposes to _____ as a recommendation in the _____ section and likewise to remove all reference to it in the _____ section of the label.

The sponsor met with the Division prior to initiating the development program for this product. Rather than require a demonstration of equivalent efficacy between 40 mg BID and 80 mg ER, the Division advised the sponsor to conduct studies to demonstrate that Lescol 80 mg ER effected superior LDL-C lowering from baseline compared to 40 mg once daily by a margin of at least 6% absolute. This margin was chosen insofar as it is consistent with the known phenomenon for the statin class of a 5-7% absolute incremental lowering in LDL-C from baseline with progressive doubling of drug dose (the so-called "rule of 7").

Of note, other regulatory authorities, according to the sponsor, required a demonstration of therapeutic equivalency between Lescol 80 mg ER and Lescol 40 mg BID. The

sponsor defined this as no greater than an absolute difference in mean percent reduction in LDL-C of 5% between the two doses.

This memo will address the phase 3 data supporting the efficacy and safety of the 80 mg ER dose, the data and analyses necessary to support the proposed change to the Indications and Usage section regarding HDL raising, and the absence of data to support from the label for Lescol (NDA 20-261).

Clinical/Statistical Efficacy

The sponsor conducted four phase 2 studies and three phase 3 studies to establish the efficacy and safety of Lescol 80 mg ER. The phase 3 studies were 6-month, randomized, blinded, active-controlled trials. These studies contributed the majority (~860) of the patients comprising the 80 mg MR safety pool (total ~ 900) for the to-be-marketed formulation. In addition, in the phase 3 trials, ~500 patients received fluvastatin 40 mg immediate release (IR) and 330 received fluvastatin 40 mg IR BID for up to 6 months across two of the trials.

The phase 3 (302, 351, 353) studies were multi-center, parallel group studies in patients with primary hypercholesterolemia or mixed dyslipidemia. The trials had four-week diet/placebo run-in periods followed by 24 weeks of active therapy. All three studies compared the LDL-lowering efficacy of Lescol 80 mg ER to Lescol 40 mg once daily, and two of the three (302, 353) also included a third arm treated with Lescol 40 mg BID.

In addition to analyses of superiority for the primary comparison between 80 ER and 40 once daily, secondary analyses to determine non-inferiority for the comparison of 80 ER and 40 BID were conducted. Pooled analyses were conducted in order to assess efficacy within relevant subgroups.

Across the three studies, Lescol 80 ER effected LDL-C lowering from baseline that was statistically significantly superior to Lescol 40 once daily by mean differences ranging from 8-10%. Additionally in studies 302 and 353, the differences in mean LDL-C lowering from baseline between Lescol 80 ER and Lescol 40 BID were +0.1 and -2.5%, respectively. Tests of non-inferiority for the difference were significant (i.e., 80 mg ER was non-inferior to the comparator). The absolute changes from baseline by treatment group were nearly identical across the studies. The effects on the other lipid parameters measured were likewise comparable by treatment group across studies. The lipid altering data from study 301, representative of the phase 3 results, are summarized below.

Study 302. Least squares mean for % change from baseline to endpoint.			
	Fluvastatin 80 mg ER N=341	Fluvastatin 40 mg IR N=174	Fluva 40 mg IR BID N=173
LDL-C	-33	-24	-33
HDL-C	8.1	6.2	6.7
LDL:HDL ratio	-36	-28	-36
Total-C	-23	-17	-24
Triglycerides	-12.3	-8.2	-13.1
Apo A1	7.8	6.5	6.4

Apo B	-25	-19	-25
-------	-----	-----	-----

The pooled efficacy analyses conducted and presented by the sponsor demonstrate that the LDL-lowering effect of Lescol, regardless of the dose or dosage form occurred early, with the majority of the effect occurring by the 2-week visit and the full effect seen by 4 weeks and maintained for the duration of the 6-month treatment period. This is consistent with previous studies of fluvastatin as well as for the rest of the statin class. The sponsor proposes to convey the timing of the effect in labeling. This is acceptable.

Review of tabular summaries in the sponsor's application summary, for the ITT population, show that the LDL-lowering effect of Lescol, across the three treatment groups studied in phase 3, was consistent across subgroups by gender, age greater than or less than 65, race (Caucasian, Black, other), and BMI greater than or less than 30.

The sponsor also presents analyses of the mean percent increase in HDL-C from baseline as a function of baseline HDL-C greater than or less than 35 mg/dL and by baseline TG (greater than or less than 200). The mean percent increases in HDL-C are greater in patients with higher baseline TG, regardless of baseline HDL-C. In addition, though based upon few patients, the HDL-raising effect also appeared greater for the subgroup with low HDL even in the setting of TG < 200 mg/dL. Because of the size of this subgroup (N=12), the data do not merit inclusion in labeling, though the observation is consistent with the known mechanisms of the low-HDL state (i.e., a TG cutoff of 200 does not exclude patients with abnormalities in the metabolism of TG-rich lipoproteins leading to low HDL-C) and with the known mechanism of action of statins.

The sponsor's proposed labeling includes a modification of the existing table summarizing the lipid altering effects of Lescol across the dosage range and maintains the previous inclusion of efficacy data in the subgroup with baseline TG > 200 mg/dL.

Finally, the proposed addition to Indications and Usage of the phrase "and to increase HDL-C" requires support, consistent with what has been required of other statins so labeled, in the form of descriptive data of the distribution of HDL-raising response, across doses. This has been accomplished by the surrogate for a cumulative distribution function, a simple enumeration of the median, 25th, and 75th percentile percent changes from baseline. These analyses have not been provided in the original submission, though they have been requested during preliminary labeling negotiations with the sponsor.

Safety

The safety exposure to Lescol XL 80 mg is adequate. Approximately 750 patients completed 6 months of therapy in the combined phase 3 studies. All told, over 900 patients received Lescol XL 80 mg in phase 2 and phase 3 trials. The total study population was approximately 50% male and over 90% Caucasian. Approximately 25% were > 65 years of age.

Statins generally and Lescol in specific are well tolerated and associated with only rare serious adverse events that have been attributed to drug. The two body systems affected by statins to cause significant concern are liver and muscle. Statins are associated with dose-dependent increases in the incidence of elevations in hepatic transaminases. These are felt to be related to the mechanism of action of the drug as an inhibitor of HMG-CoA reductase. A clinically significant elevation has traditionally been defined as an elevation to greater than 3X ULN on two consecutive occasions at least a week apart. These elevations often resolve without any intervention and are almost always completely reversible on reduction in dose or discontinuation of drug. The incidence of serious hepatic disease (liver failure) associated with statin use, estimated based on spontaneous reports to FDA, is very low and does not exceed the background rate in the general population. While it is impossible to exclude the possibility that statins, Lescol included, may in rare instances cause serious liver disease, there is likewise no compelling evidence that there is a tangible risk of this occurrence.

Statins are also known to cause, in rare instances, serious muscle injury, including frank rhabdomyolysis with myoglobinuric renal failure. This, too, is felt to be related to the pharmacology of the drug as an inhibitor of HMG-CoA reductase in the muscle cell. Risk factors for this adverse event include concomitant use of drugs or foods that increase systemic levels of active drug, individual susceptibility, and pharmacodynamic drug interactions leading to a synergistic effect at the level of the muscle. These events are too rare to define a relationship to dose, and cases have been seen in patients taking low, intermediate, or high doses of the marketed drugs.

Transaminase elevations

The current labeling for Lescol cites rates of consecutive > 3X ULN elevations in transaminases of 0.2, 1.5, and 2.7% for the 20, 40 and 80 (40 BID) mg doses, respectively from the pooled placebo-controlled trials database. For the 80 mg ER dosage strength, the pooled phase 2 and 3 data show a 1.9% rate of clinically significant transaminase elevations. Across these same studies, the rate of such elevations for the 40 mg IR BID groups was 4.3%, suggesting that the 80 mg ER dosage form may have less of a tendency to cause transaminase elevations. For the phase 3 trials alone, the incidence of consecutive elevations in transaminase of > 3 X ULN was 4.9% for the 40 BID group and 1.9% for 80 mg ER group. This difference was nominally statistically significant, though the lower bound of the 95% confidence interval for the difference in rates was 0.5%. In addition, review of the LFT data from the two phase 3 trials that included a 40 BID arm shows that the majority of the cases were from study 353, in which 7.2% of the 40 BID patients experienced this AE as compared to 1.4% of the 80 ER patients. By contrast, in study 302, the incidences for these two treatment groups were 2.9 and 1.5%, respectively. One patient in study 302 on 40 BID underwent

cholecystectomy, suggesting a possible role of biliary disease in her transaminase elevations, though her LFTs did not return to normal until after discontinuation of drug. Finally, as mentioned above, the historical experience in the placebo-controlled trials of Lescol 40 BID reviewed as part of S-006 shows a rate of clinically significant transaminase elevations of 2.7%. In discussions with the sponsor, I am reminded that the designs of the trials for that supplement involved titration to the maximum dose of 40 BID. The trials reviewed for the current NDA all involved initiation of therapy at the full dose to be studied, whether 40 QD, 40 BID, or 80 ER. The majority of the elevations observed in the current database (>80%) were first noted within the first 12 weeks of therapy. In conclusion, it is not clear that the observed difference denotes a true difference in the tendency of the two dosages (40 BID vs. 80 ER) to cause transaminase elevations and therefore a clinically relevant difference in the safety profiles. Overall, the 40 BID dosage still appears to be safe as well as effective as both a starting dose and after titration. The LFT data will need to be conveyed in labeling.

Elevations in creatine kinase

There were two cases in the phase 2 and 3 trials of marked (> 10 X ULN) CK elevations, an indicator of skeletal muscle toxicity of drug, and these were both in the 40 mg IR group. There were no cases of rhabdomyolysis. The frequency of elevations in CK to lesser degrees was consistent across the Lescol dosage groups. The incidence of musculoskeletal disorders was similar across the Lescol treatment groups, affecting 13-20% of patients.

No unexpected safety issues are raised by the outcomes of the Lescol XL development program. The phase 2 and 3 studies of Lescol 80 mg XL were conducted with this as the starting dose (no titration phase). From these studies, it is apparent that Lescol 80 mg XL is a safe starting dose of fluvastatin in patients requiring reductions in LDL-C of over 30% from baseline to goal. As stated above, the incidence of LFT abnormalities using the doses studied as starting doses should be conveyed in labeling under WARNINGS.

DSI

Three study sites were inspected. No violations were observed that would affect the reliability or integrity of the data submitted in support of the NDA.

Financial disclosure

Two investigators (principal investigator and subinvestigator from the same institution) had financial information to disclose. Together they had received more than \$25,000 for recurrent CME activities from Novartis. Financial disclosure information was received from the great majority of the clinical investigators involved in the studies submitted to this NDA. The sponsor has certified that there were no arrangements made with regard to outcome payments, that no investigator disclosed a proprietary interest in the product or any significant equity interest in Novartis. The information provided suggest no reason to question the integrity of the data submitted.

Biopharmaceutics

OCPB has recommended approval. The pharmacokinetic studies of Lescol XL do demonstrate a peak concentration of fluvastatin at 3 hours, in contrast to Lescol capsules, which produce a peak at 1 hour. Labeling has been negotiated. No phase 2 commitments are required.

Chemistry

ONDC has recommended approval pending an acceptable establishment inspection. Five inspections have been conducted, the last on September 28, 2000. All but the last were deemed acceptable. The last report is pending as of 10-4-00.

Pharmacology/Toxicology

There were no preclinical data submitted with this NDA as previously agreed between FDA and the sponsor.

Nomenclature: OPDRA consult

OPDRA expressed concern that the product may not actually be an extended release formulation, noting that it is to be dosed once daily, as are the 20 and 40 mg dosage strengths of Lescol capsules when administered singly. However, the labeling reviewed by OPDRA

As noted above, the 40 BID dose and the 80 XL QD dose yield nearly equivalent mean % reductions in LDL-C from baseline. OPDRA did not have any objection to the XL suffix *per se*, as long as the dosing interval for the XL form is less frequent than that for the immediate release form. This is the case for the administration of 80 mg of fluvastatin daily, as above.

Labeling

As discussed above, the data describing the efficacy of Lescol-80 mg XL in the treatment of hypercholesterolemia should be added to the existing efficacy tables in the label. As such, the existing indications for the use of Lescol will pertain to this new dosage form as well. The addition to the Indications and Usage section of the proposed language reflecting the expected increases in HDL-C are acceptable. This is supported not only by the finding of significant mean or median elevations from baseline in HDL-C in the 80 XL groups but also by an enumeration of the median, 25th, and 75th percentiles in percent change from baseline in HDL-C from the pooled studies of 80 mg ER in the text of the Clinical Studies subsection of the label. The sponsor wishes to combine the labels for Lescol capsules (NDA 20-261) and Lescol XL. Combining the labels requires that the sponsor submit a labeling supplement requesting this change to the NDA for Lescol capsules (NDA 20-261). This supplement can be approved simultaneously with NDA 21-192. Supplement S-025 of NDA 20-261, proposing changes to the Lescol label regarding HDL-C raising, has not been reviewed at this time. Inclusion of the data on distribution of HDL-C responses across the approved dosage range for Lescol capsules awaits approval of this supplement. The revisions to the safety information are acceptable.

As discussed above,

The 40 mg BID recommended dose was approved based upon review of data supporting its safety and effectiveness. The current application contains further data on safety and efficacy from the trials conducted to support the registration of 80 mg ER. The incidence of consecutive transaminase elevations was higher among the pooled 40 mg BID patients than in the comparator groups (80 XL and 40 IR per day). However, the observed difference was largely driven by the results of one of the two studies that yielded a result markedly different than that seen historically with the 40 BID dose. There is no good evidence, therefore, that the 40 BID dose is demonstrably less safe than the 80 mg XL dose. Therefore, the former should remain a recommended dose of Lescol.

This position has been conveyed to the sponsor.

Finally, the data submitted support the use of Lescol 40 mg BID as an optional starting dose of fluvastatin. The sponsor has proposed to recommend Lescol 40 QD or 80 XL as starting doses for patients requiring $\geq 25\%$ LDL-C lowering from baseline to goal. The 40 BID dose should also be recommended as an option for this group. This has been conveyed to the sponsor.

Conclusions

The sponsor has conducted adequate and well-controlled studies of Lescol 80 mg XL and has established that it is a safe and effective dosage form and strength of fluvastatin sodium. No new safety concerns are raised by this application. One establishment inspection is still pending. The application should be approved once labeling can be finalized and the report of an acceptable establishment inspection received.

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
HFD-510

Recommendation code: AP

CC:
NDA 21-192 Arch
HFD-510

LSI
10-6-00

Lescol[®] (fluvastatin sodium) Capsules
Lescol XL[®] (fluvastatin sodium) Extended Release Tablets

NDA 21-192

US Package Insert

**Division of Metabolic and
Endocrine Drug Products**
Proposed revisions

September 18, 2000

Property of Novartis Pharmaceuticals
Confidential
May not be used, divulged, published or otherwise disclosed
without the consent of Novartis Pharmaceuticals

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

WITHHOLD 3 PAGE (S)

New Drug Application Filing Memorandum

JAN 27 2000

Office of Clinical Pharmacology and Biopharmaceutics

NDA:	21-192	Priority Classification:	S		
IND:		Indication:	Hypercholesterolemia		
Brand Name:	Lescol [®]	Submission Date:	12/09/99		
Generic Name:	Fluvastatin sodium	Route of Administration:	PO		
Chemical Type:		UFGD:			
Sponsor:	Novartis	Review Division:	HFD-870		
Reviewer:	Xiaoxiong (Jim) Wei, Ph.D.	Medical Division:	HFD-510		
Team Leader:	Hae-Young Ahn, Ph.D.				
Items Included in NDA (CTD)		Yes	No	Request	
Table of Contents present and sufficient to locate reports, tables, data, etc.		X			
Tabular Listing of All Human Studies		X			
HPK Summary		X			
Study Synopses		X			
Labeling		X			
Bioavailability and Bioequivalence Studies:					
ADME Study -		X			
BA Studies - Absolute BA Relative BA			X		
BE Studies - Average BE Population BE Individual BE			X		
Food-Drug Interaction Study		X			
In Vitro-In Vivo Comparison (IVIVc) Studies			X		
Reference Bioanalytical and Analytical Methods		X			
Dissolution Profiles		X			
Studies Using Human Biomaterials			X		
Plasma Protein Binding Studies			X		
Metabolism Studies Using Hepatocytes, Microsomes, etc.			X		
Blood / Plasma Ratio			X		
Human Pharmacokinetics (PK) Studies:					
PK and Initial Safety and Tolerability in <u>Healthy</u> Volunteers - Single Dose Multiple Dose		X			
PK and Initial Safety and Tolerability in <u>Patient</u> Volunteers - Single Dose Multiple Dose		X			
Dose Proportionality - Single Dose Multiple Dose		X			
PK in Population Subsets to Evaluate Intrinsic Factor Effects - Ethnicity Gender Pediatrics			X		

Geriatrics Renal Impairment Hepatic Impairment			
PK in Population Subsets to Evaluate Extrinsic Factor Effects - In-Vivo Effects <u>on</u> Primary Drug In Vivo Effects <u>of</u> Primary Drug In-Vitro Drug Interaction		X	
Population PK Studies		X	
Summary of PK / PD Studies		X	
PK / PD Studies in Volunteers		X	
PK / PD Studies in Patients		X	
Individual Datasets for all PK and PK / PD Studies in Electronic Format		X	
Other:			
Genotype / Phenotype Studies		X	
Chronopharmacokinetics		X	
Literature - Number of Articles Sufficient		X	
Which Phase IV Studies Requested?			
1.			
2.			
3.			

Briefing In Content:

Fluvastatin sodium (Lescol[®], SDZ XUO 320) is a potent synthetic competitive inhibitor of hydroxymethylglutaryl-CoA reductase (HMGR), the enzyme responsible for converting 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor for cholesterol.

Fluvastatin undergoes first pass metabolism, which begins to show non-linear kinetics (competitive inhibition) at doses higher than 20 mg and result in higher than expected systemic concentrations at higher doses. Although fluvastatin undergoes extensive metabolism only the parent drug, fluvastatin, is the active moiety and its metabolites are not considered to be active. Fluvastatin has a short elimination half-life (1.5-2 h). Currently, the approved dose of Lescol[®] is 20-80 mg per day. Usually, doses at or below 40 mg are taken once a day at bedtime. Doses of 80 mg are to be taken in divided doses (40- mg twice a day).

The MR formulation delivers fluvastatin at a slower rate than the conventional immediate release (IR) capsule; thus reducing first pass saturation resulting in lower systemic exposure. This, in turn, should allow for a higher dose with increased efficacy and tolerability of fluvastatin. An 80- mg MR tablet was developed and studied for its safety and efficacy in hyperlipidemic patients.

A total of four human pharmacokinetic studies were conducted to characterize fluvastatin MR (Lescol XL) tablets:

Phase 1:

Study W 251: This was a crossover, single -dose study to evaluate three 80 mg fluvastatin modified release (MR) dosage forms which were different in their release rates.

Study W 252: This study also was to assess the release nature of three other fluvastatin MR formulations relative to the commercial IR capsule (Lescol[®]).

Study W 351: This study assessed the effect of food on the pharmacokinetics of the fluvastatin 80 mg MR tablet.

Phase 2:

Study W 253: This was a placebo controlled, multiple-dose, parallel group blinded safety and tolerability study of escalating doses (80, 160, 320 and 640 mg) of fluvastatin MR in hypercholesterolemia patients.

This Application is fileable.

Comments to be sent to Sponsor:

Please submit the detailed data sets of dissolution profiles.

LSI
Xiaoxiong (Jim) Wei, Ph.D.; EDA / CDER / OPS / OCPB / DPE-II

LSI 4/27/00
Hae-Young Ahn, Ph.D., Team Leader; FDA / CDER / OPS / OCPB / DPE-II

CC: NDA 21-192, HFD-510 (Simoneau, Shen), HFD-850 (Lee), HFD-870 (Huang, Ahn, Wei), CDR (MurphyB)

ORIGINAL

Meeting Minutes

**Division of Metabolic and Endocrine Drug Products
IND**

Date: Thursday, September 16, 1999

Location: Parklawn 1456

Time: 2:00 to 3:00 PM

Format: Teleconference

FDA Attendees:

Dr. Orloff

Dr. Shen

David Hoberman

M. Simoneau

Novartis Attendees:

Dr. Gonasun

Dr. Blasetto

Jerry Klimek

1. Meeting Objective

This was a telephone conference requested by the sponsor to discuss the proposals in the General Correspondence submitted for Lescol IND No. _____ date-submitted July 14, 1999.

2. Discussion Points and Decisions

Enclosure 1, fax submitted September 14, 1999, are the proposed agenda questions.

Discussion and responses to the agenda questions are included in your meeting minutes, faxed October 1, 1999 (enclosure 2). These minutes have been reviewed by FDA attendees with no additional corrections or notations.

Post-meeting note:

There was an additional comment on the July 14, 1999 submission regarding the content and format of the Lescol 80 mg XL. Biopharmaceutics may need raw data and pk analysis electronically but this can wait until filing.

Minutes preparer: M. Simoneau LS

Concurrence Chairman: Dr. Orloff LS

10-15-99

10-15-99 (for Dr. Orloff)

Initialed by: D.Hoberman 10.14.99/S.Shen (no response)

cc: Original IND _____ Div Files

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

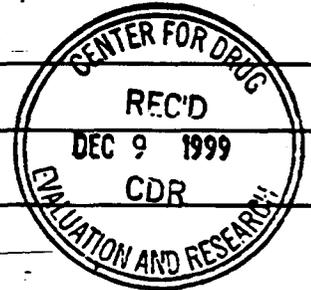
21-192

APPLICATION INFORMATION

NAME OF APPLICANT NOVARTIS PHARMACEUTICALS CORPORATION	DATE OF SUBMISSION December 8, 1999
TELEPHONE NO. (Include Area Code) (973) 781-8145	FACSIMILE (FAX) Number (Include Area Code) (973) 781-3590
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 59 Route 10 East Hanover, New Jersey 07936-1080	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-192	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) fluvastatin sodium	PROPRIETARY NAME (trade name) IF ANY Lescol XL[®]
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)	CODE NAME (if any)
DOSAGE FORM: Extended Release Tablets	STRENGTHS: 80 mg
ROUTE OF ADMINISTRATION: Oral	
(PROPOSED) INDICATION(S) FOR USE: Treatment of hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidemia And Treatment to slow the progression of coronary atherosclerosis in patients with coronary heart disease	



APPLICATION INFORMATION

APPLICATION TYPE (check one)	
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA-AADA, 21 CFR 314.94)
<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> -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)	
<input checked="" type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> SUPAC SUPPLEMENT
<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
<input type="checkbox"/> OTHER	
REASON FOR SUBMISSION	
PROPOSED MARKETING STATUS (check one)	
<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED 57	THIS APPLICATION IS <input type="checkbox"/> PAPER <input checked="" type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> 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.

See Attached

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

See Attached

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

X	1. Index
X	2. Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	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)
X	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)
X	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))
X	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)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
X	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)
X	16. Debarment certification (FD&C Act 306 (k) (1))
X	17. Field copy certification (21 CFR 314.50 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	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 reviewed and, to the best of my knowledge 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 <i>Jerry Klimek</i>	TYPED NAME AND TITLE Jerry Klimek, Associate Director Drug Regulatory Affairs	DATE Dec. 8, 1999
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ADDRESS (Street, City, State, and ZIP Code) 59 Route 10 East Hanover, New Jersey, 07936-1080	Telephone Number (973) 781-8145
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DHHS, Reports Clearance Officer
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Hubert H. Humphrey Building, Room 531-H
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Washington, DC 20201

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