CENTER FOR DRUG EVALUATION AND RESEARCH

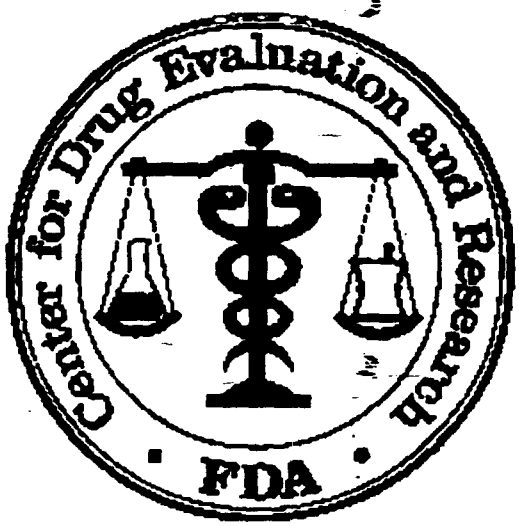
APPLICATION NUMBER:

21-192

CORRESPONDENCE

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE October 6, 2000



Comments:

Attached is a letter from the Division regarding NDA 21-192 and NDA 20-261/S-028. The original will follow by mail.

Please don't hesitate to call with any questions.~Bill

TO:	**FROM:**
Name: Adrian L. Birch	**Name:** William C. Koch, R.Ph.
Executive Director, Drug Regulatory Affairs	Regulatory Project Manager
Fax No.: (973) 781-3590	**Fax No.:** (301)-443-9282
Phone No.: (973) 781-3589	**Phone No.:** (301)-827-6412
Location: Novartis Pharmaceuticals Corp.	

Pages (including this cover sheet): four (4)

NDA 21-492
Lescol (fluvastatin sodium) capsules
Lescol XL (fluvastatin sodium extended release tablets), 80 mg

The preceding Action Letter has been reviewed by the undersigned:

Name	Discipline	Signature	Recommended Action	Date
S. Shen, M.D.	Medical Officer			
Mary Parks, M.D.	Acting Medical Team Leader			
K. Davis-Bruno, Ph.D.	Pharmacology Team Leader			
S. Kelly, Ph.D.	Chemist			
S. Moore, Ph.D.	Chemistry Team Leader I			
P. Hepp, Ph.D.	Biopharmaceutics			
H. Ahn, Ph.D.	Biopharmaceutics Team Leader			
T. Sahlroot, Ph.D.	Biometrics 2 Team Leader			
E. Galliers	Chief, Project Mgt. Staff			
D. G. Orloff, M.D.	Division Director	GST	AP	10-6-00

NDA 21-192
Lescol XL (fluvastatin sodiumextended release tablets), 80 mg

The preceding Action Letter has been reviewed by the undersigned:

Name	Discipline	Signature	Recommended Action	Date
S. Shen, M.D.	Medical Officer			
D. Orloff, M.D.	Medical Team Leader			
K. Davis-Bruno, Ph.D.	Pharmacology Team Leader			
S. Kelly, Ph.D.	Chemist			
S. Moore, Ph.D.	Chemistry Team Leader I			
P. Hepp, Ph.D.	Biopharmaceutics			
H. Ahn, Ph.D.	Biopharmaceutics Team Leader			
T. Sahlroot, Ph.D.	Biometrics 2 Team Leader			
E. Galliers	Chief, Project Mgt. Staff	LSC reviewed w/o MOR, Biopharm review, Peds. Pg, Ph. 4 comm. timelines, or SUR, EER		04.26.00
D. G. Orloff, M.D.	Division Director			

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: September 15, 2000

Comments:

Attached are initial comments regarding labeling for NDA 21-192.

The attached does not represent the Division's final label comments.

Please don't hesitate to call with any questions.~Bill

TO:	**FROM:**
Name: Adrian L. Birch	**Name:** William C. Koch, R.Ph.
Executive Director, Drug Regulatory Affairs	Regulatory Project Manager
Fax No.: (973) 781-3590	**Fax No.:** (301)-443-9282
Phone No.: (973) 781-3589	**Phone No.:** (301)-827-6412

Location: Novartis Pharmaceuticals Corp.
Pages (including this cover sheet): transmission one = fourteen (14)

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

NDA 21-192

US Package Insert

Author(s):	Jerry Klimek
Document type:	Package Insert Template
Document status:	Final Draft
Release date:	November 29, 1999
Number of pages:	20

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

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: October 6, 2000

Comments:

Attached are comments regarding
Dissolution limits for NDA 21-192.

Please don't hesitate to call with any questions.~Bill

TO:	**FROM:**
Name: Adrian L. Birch	**Name:** William C. Koch, R.Ph.
Executive Director, Drug Regulatory Affairs	Regulatory Project Manager
Fax No.: (973) 781-3590	**Fax No.:** (301)-443-9282
Phone No.: (973) 781-3589	**Phone No.:** (301)-827-6412
Location: Novartis Pharmaceuticals Corp.	

Pages (including this cover sheet): Two (2)

NDA 21-192
Lescol XL (fluvastatin sodium extended release tablets), 80mg
Novartis Pharmaceuticals Corporation

We refer to your submission concerning your proposed dissolution limits for Lescol XL. The following recommendation was submitted by Paul Hepp, Ph.D. of the Office of Clinical Pharmacology and Biopharmaceutics:

In Vitro Dissolution

The sponsor's rationale for choosing the apparatus, media, and sampling times appear to be sound. However, OCPB requires that dissolution specifications be set based on the lots that were used in the bioavailability studies (lots H05018 and T115195) which were also of the same formulation of that used in the clinical studies. Based on this rationale, the 2 and 4 hour sponsor proposed specifications are excessively wide and OCPB recommends a 2 hour specification of —— and a 4 hour specification of —— OCPB agrees with the 0.5 and 8 hour specifications of —— respectively.

OCPB recommended dissolution limits for fluvastatin sodium MR tablet

Time	Drug released
0.5 hours	——
2 hours	——
4 hours	——
8 hours	——

If you have any questions, you may contact William C. Koch, R.Ph., Regulatory Project Manager at (301) 827-6412.

CLEARED FOR FAXING: [signature] 10/6/00

Hae-Young Ahn, Ph.D. Date
Biopharmaceutics Team Leader

Adrian L. Birch
Executie Director
Drug Regulatory
Affairs

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936-1080
Tel 973-781-3589
Fax 973-781-3590
Internet: adrian.birch
@pharma.novartis.com

NOVARTIS

Fax

To Mr. William Koch
Senior Regulatory Manager
Division of Metabolic and Endocrine Drug Products
HFD-510

Fax No. 301-443-9282

Date October 5, 2000

No. of Pages 5

Re: NDA No. ~~21-~~192
Lescol XL® (fluvastatin sodium) Tablets

Dear Mr. Koch:

As we discussed, I am providing you with current versions of our draft container labels and cartons for Lescol® XL (fluvastatin sodium).

Sincerely,

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

Attachments

Adrian L. Birch
Executie Director
Drug Regulatory
Affairs

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, New Jersey 07936-1080
Tel 973-781-3589
Fax 973-781-3590
Internet: adrian.birch
@pharma.novartis.com

NOVARTIS

Fax

To Mr. William Koch
Senior Regulatory Manager
Division of Metabolic and Endocrine Drug Products
HFD-510

Fax No. 301-443-9282

Date October 5, 2000

No. of Pages 20

Re: NDA No. 21-192
Lescol XL® (fluvastatin sodium) Tablets

Dear Mr. Koch:

Reference is made to our pending NDA 21-192 for Lescol® XL (fluvastatin sodium).

At this time we are providing you with a copy of our draft package insert which contains all requested revisions.

Sincerely,

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

Attachments

Donna Kapples
Assistant Director
DRA-CMC

Novartis Pharm. Inc.

Tel (973) 781-6929
Fax (973) 781-6325
Internet: donna.kapples
@pharma.novartis.com

NOVARTIS

Fax

Attention: Mr. Bill Koch

Fax no.: (301) 443-9282
Number of pages: 3 including cover page

Date: 28-Sep-00

Concerning: **Individual dissolution data, batch H-05018/Lescol XL Tablets/pending NDA 21-192**

Dear Mr. Koch,

As per the teleconference of 27-Sep-00, please find attached the individual dissolution data points for batch H-05108.

If there are any other questions, I can be reached at (973) 781-6929.

Sincerely,

Donna Kapples

Donna Kapples
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

NOVARTIS
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Response:

Tables 1 and 2 provide the individual tablet data obtained for Lescol XL Tablets, 80 mg, batch number H-05018, used in clinical study W251. The data presented in Table 1 were obtained using the official methodology at time of batch release (version A in Table 3). Additionally, data are also provided in Table 2 using the dissolution methodology filed in the application (version C). Table 3 describes the three versions of the dissolution method used during the development process.

Table 1. Dissolution data for Lescol XL Tablets, 80 mg, batch no. H-05018, using method version A

	Cumulative percent release						
Tablet no.	0.5 hrs.	1 hr.	2 hrs.	4 hrs.	8 hrs.	12 hrs.	16 hrs.
1							
2							
3							
4							
5							
6							
Average	3.3	6.6	12.8	24.9	48.7	71.6	88.0
RSD (%)	23.4	22.1	22.7	22.6	22.9	22.8	16.5

Table 2. Dissolution data for Lescol XL Tablets, 80 mg, batch no. H-05018, using method version C

	Cumulative percent release[1]			
Tablet no.	0.5 hrs.	2 hrs.	4 hrs.	8 hrs.
1				
2				
3				
4				
5				
6				
Average	6.6	26.3	60.1	102.7
RSD (%)	7.4	3.8	4.9	1.3

[1]Data from 24 month stability at 25°C/60%RH stored in a white — bottle with —

Table 3. Dissolution methods for Lescol XL Tablets, 80 mg

Parameter	Version A	Version B	Version C
Apparatus			
Rotation speed			
Medium			
Temperature	37 ± 0.5°C	37 ± 0.5°C	37 ± 0.5°C
Volume			

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: September 20, 2000

Comments:

Attached are comments from the biopharmaceutics team regarding NDA 21-192.

Please don't hesitate to call with any questions.~Bill

TO:
Name: Adrian L. Birch
Executive Director, Drug Regulatory Affairs
Fax No.: (973) 781-3590
Phone No.: (973) 781-3589
Location: Novartis Pharmaceuticals Corp.
Pages (including this cover sheet): Two (2)

FROM:
Name: William C. Koch, R.Ph.
Regulatory Project Manager
Fax No.: (301)-443-9282
Phone No.: (301)-827-6412

NDA 21-192
Lescol XL (fluvastatin sodium extended release tablets) 80mg
Novartis Pharmaceuticals Corporation

In regard to the above referenced new drug application, this Division's Biopharmaceutics team submits the following comments related to dissolution data:

The sponsor's rationale for choosing the apparatus, media, and sampling times appear to be sound. However, since the individual and mean dissolution data for the batches used in study W251 and W351 as well as pivotal clinical trials have not been submitted in the Pharmacokinetics Section of the application, the appropriateness of the proposed dissolution specifications cannot be evaluated.

The sponsor should submit this data for review by the Office of Clinical Pharmacology and Biopharmaceutics.

If you have any questions, you may contact William C. Koch, R.Ph., Regulatory Project Manager at (301) 827-6412.

CLEARED FOR FAXING HST 9/20/00

Hae-Young Ahn, Ph.D.. Date
BiopharmaceuticsTeam Leader

Lisa N. Pitt, Pharm.D.
Assistant Director

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs

Tel (973) 781-3279
Fax (973) 781-3590
Internet: lisa.pitt@pharma.novartis.com

NOVARTIS

Fax

Attention: Bill Koch
Senior Regulatory Manager
HFD-510

Fax no.: 301 443-9282
Number of pages: 5 including cover page

Date: July 28, 2000

Concerning: Lescol XL Container & Bottle Label Mock-up

Dear Bill,

Attached please find the Lescol XL for the bottles and carton label mock-ups, as previously requested. Color copies will be provided to you early next week

Please contact me should you have any questions.

Regards,

Lisa N. Pitt, Pharm.D.

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

NDA 21-192
Lescol (fluvastatin sodium)
Novartis

Biopharmaceutics review request:

Please submit the detailed data sets of dissolution profiles.

Cleared for faxing by: _____ 2/18/00

MAY 2 4 2000

NDA 21-192

Novartis Pharmaceutical Corporation
Attention: Mr. Adrian L. Birch
Executive Director
Drug Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936-1080

Dear Mr. Birch:

Reference is made to your correspondence dated March 21, 2000, requesting a waiver for pediatric studies under 21 CFR 314.55(c) for your pending new drug application for Lescol XL (fluvastatin sodium) Extended Release Tablets.

We have reviewed the information you have submitted and agree that a waiver of the requirement to evaluate the use of this product in patients under the age of 10 years is justified.

Accordingly, under 21 CFR 314.55, we are granting you a waiver of the requirement for pediatric studies in patients under the age of 10 at this time.

Your letter also inquired as to the data required for purposes of pediatric labeling (21 CFR 201.57(f)(9). We require the same data as those required for pediatric exclusivity. The data should derive from studies enrolling both boys and girls with heterozygous familial hypercholesterolemia.

If you have questions, please contact Margaret Simoneau, Regulatory Project Manager, at (301) 827-6418.

Sincerely,

JK

John K. Jenkins, M.D.
Acting Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 21-192

DEC 15 1999

Novartis Pharmaceuticals Corporation
Attention: Jerry Klimek
Associate Director, Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Dear Mr. Klimek:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Lescol XL® (fluvastatin sodium extended release) Tablets, 80 mg
Therapeutic Classification:	Standard (S)
Date of Application:	December 8, 1999
Date of Receipt:	December 9. 1999
Our Reference Number:	NDA 21-192

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 7, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 9, 2000, and the secondary user fee goal date will be December 9, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not

granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely,

ES 12.15.99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

Tel 973 781 7500
Fax 973 781 3590

NOVARTIS NDA NO. 20261 REF NO. 028
NDA SUPPL FOR SLR

October 6, 2000

David Orloff, MD
Director
Division of Metabolic and Endocrine
Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-261
Lescol® (fluvastatin sodium)
Capsules

Labeling Supplement

Dear Dr. Orloff,

Reference is made to our pending NDA 21-192 for Lescol® XL (fluvastatin sodium) extended-release tablets. As you know, as a consequence of agency preference, we have created a combined package insert that contains information relevant to Lescol® (fluvastatin sodium) capsules as well as Lescol XL.

As a result of that initiative, we hereby request that our existing package insert for Lescol capsules be revised to incorporate all of the new labeling entries for Lescol XL which have been mutually agreed upon as part of the approval process for the new formulation.

If you have any questions or comments regarding this request, please contact me at 973 781 3589.

Sincerely,

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

Sent via Facsimile

October 3, 2000

David Orloff, MD
Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-192

Lescol® XL (fluvastatin sodium) Tablets

Response to FDA Request for Information

Dear Dr Orloff

This correspondence is being sent to you in response to our discussion today, in which we talked about issues associated with transaminase (TA) elevations in patients who were treated with Lescol capsules 40mg bid.

You inquired about possible explanations to address why the incidence of TA elevations was higher for 40mg bid in our Lescol XL database than the historical Lescol capsule database. We informed you that a general consideration involves the fact that in the Lescol capsule database patients were titrated to 40mg bid whereas in the Lescol XL clinical program they were treated *de novo*.

We were asked to review our pivotal trials to determine if one of them was an outlier, which skewed the rate of TA elevations. I have attached selected pages from our three pivotal studies, and they indicate that the rate was 7.2% in Protocol 353.

A request was made to calculate confidence intervals for the incidence of elevations observed on Lescol XL versus Lescol capsules 40mg bid. That analysis is attached.

In response to your general guidance, we prepared a tabular summary derived from patient narratives provide in our NDA such that you might assess possible factors which contributed to different rates of occurrence for TA elevations.

Finally, we have attached revised text for the Liver Enzyme section of our draft package insert, which addresses the different rates we encountered.

Please call me at (973) 781-3589 if you need to clarify any aspect of this matter.

Sincerely,

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

Attachments
Submitted in duplicate

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

ORIGINAL
ORIG AMENDMENT
30.C

September 26, 2000

Shiao Wei Shen, MD
Medical Review Officer
Division of Metabolic and Endocrine
Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-192

Lescol® XL (fluvastatin sodium)
Tablets

Dear Dr. Shen,

As requested during our telephone conversation September 22, 2000, I am providing you with copies of recent references citing the study of hydroxymethylglutaryl coenzyme A (HMG0CoA) reductase inhibitors in pediatric patients with heterozygous familial hypercholesterolemia.

I have also enclosed for your convenience a copy of the letter received from the Division granting a waiver of the requirement for pediatric studies in patients below age 10.

I hope this information will assist in your review of our Pediatric Proposal Study Request submitted August 25, 2000. Please contact me at (973) 781-3279 should you require additional information or have further questions.

Sincerely,

Lisa N. Pitt, PharmD
Assistant Director
Drug Regulatory Affairs

LNP/kp
Attachments
Submitted in duplicate to David Orloff, MD, HFD-510

NOVARTIS

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

Tel 973 781 7500
Fax 973 781 3590

September 7, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-192

Lescol® XL (fluvastatin sodium) Tablets

SAFETY UPDATE

Dear Dr. Jenkins:

Reference is made to our pending NDA 21-192 for Lescol® XL (fluvastatin sodium) Tablets. At this time we are providing you with an additional safety update which supplements the data contained in the 120-Day Safety Update we submitted on April 6, 2000. The cutoff date for data included in the 120-Day report was December 31, 1999. This second safety update contains new information we generated between January 1, 2000 and May 31, 2000.

The safety profile for Lescol® XL 80 mg tablets, as presented in the attached report, is similar to both the data contained in the Integrated Summary of Safety in our original NDA, and the 120-Day Safety Update. This information further supports a favorable risk/benefit profile for administering Lescol® XL 80 mg to patients with primary hypercholesterolemia and mixed dyslipidemia.

If you have any questions or comments regarding this matter, please call me at (973) 781-3589.

Sincerely,

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

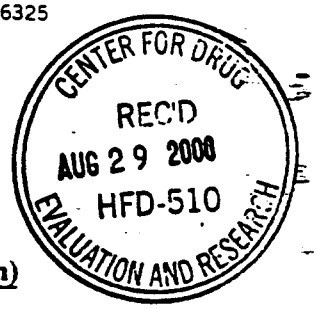
ALB/kp
Attachments
Submitted in duplicate

NOVARTIS

ORIGINAL
ORIG AMENDMENT
BM

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

Tel 973 781 7500
Fax 973 781 6325



August 25, 2000

Shiao Wei Shen, MD
Medical Review Officer
Division of Metabolic and Endocrine
Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-192

Lescol® XL (fluvastatin sodium) Tablets

Dear Dr. Shen:

Reference is made to our pending NDA 21-192 for Lescol® XL (fluvastatin sodium) Tablets.

In response to a recent request you made, we are providing you with supplementary patient narratives. These narratives pertain to individuals who enrolled in one of our three pivotal studies (Protocols 302, 351 and 353) and who had a notable abnormality of a secondary safety laboratory parameter during their participation in those studies. Narratives describing these events were not prepared for our original NDA, which is consistent with agreements reached during pre-NDA negotiations with respect to the content and format of our NDA.

As agreed with you, these narratives have only been prepared for patients who were treated with Lescol XL 80 mg. Also, we did not prepare narratives for patients with previously existing abnormalities which did not worsen signficantly while they were on Lescol XL therapy. Further, because the narratives are a representative summary of relevant facts pertaining to each patient, no case report forms or other source documents are being provided to supplement the narratives.

If you have any questions regarding this matter, please contact me at (973) 781-3589.

Sincerely,

Adrian L. Bisch
Executive Director
Drug Regulatory Affairs

ALB/kp
Attachments

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

August 8, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-192

Lescol® XL (fluvastatin sodium) Tablets

Dear Dr. Jenkins:

Reference is made to our pending NDA 21-192 for Lescol® XL (fluvastatin sodium) Tablets. One of the indications being sought in our NDA provides for reductions in triglycerides, and Dr. Shen recently made a verbal request for supplementary analyses of our triglyceride data. He explained that your Division is now establishing a requirement to present triglyceride data for the 25th, 50th and 75th percentiles. We are now providing the requested analyses of our triglyceride data.

If you have any questions or comments regarding this matter, I would appreciate it if you would contact me at (973) 781-3589.

Sincerely,

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

ALB/kp
Attachments
Submitted in duplicate
Desk copies: Mr. William Koch
Dr. Shen

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

August 7, 2000

Mr. William Koch
Senior Regulatory Manager
Division of Metabolic 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. 21-192

Lescol® XL (fluvastatin sodium) Tablets

Response to Request for Information

Dear Mr. Koch:

Reference is made to your reeent request for information pertaining to pending applications in your Division.

With respect to NDA 21-192 for Lescol® XL (fluvastatin sodium), we are providing you with a disk which contains our draft package insert.

Regarding our pending drug interaction supplement for Lescol® capsules, we are providing you with two copies of volume one for that SNDA.

If we can be of any further assistance, please do not hesitate to call.

Sincerely,

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

ALB/kp
Attachments

NOVARTIS

DUPLICATE
ORIG AMENDMENT
bl

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

Tel 973 781 7500
Fax 973 781 6325

August 2, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

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

DRAFT LABELING

Dear Dr. Jenkins:

Reference is made to our pending NDA 21-192 for Lescol® XL (fluvastatin sodium) tablets. As requested on July 24, 2000, we are providing draft copies of:

- the sample carton
- sample bottle labels
- 30 count bottle labels
- 100 count bottle labels

Please contact me at (973) 781-3279 should you have any questions or comments regarding this matter.

Sincerely,

Lisa N. Pitt, PharmD
Assistant Director
Drug Regulatory Affairs

LNP/kp
Attachments
Submitted in duplicate

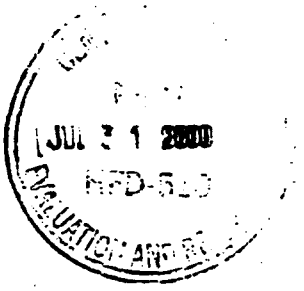
ORIG AMENDMENT
BM

COPY 1

NOVARTIS

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

Tel 973 781 7500
Fax 973 781 6325



July 27, 2000

Shiao Wei Shen, MD
Medical Review Officer
Division of Metabolic 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. 21-192

Lescol® XL (fluvastatin sodium) Tablets

Dear Dr. Shen:

We enjoyed the opportunity to discuss issues associated with your review of our referenced pending NDA yesterday. As we discussed, I am providing you with review copies of three volumes from our NDA which contain our Integrated Summary of Safety and our Integrated Summary of Efficacy. Please note that we made revisions to the presentations of age demographic data in the ISS as you requested.

I hope this information will facilitate your review. Please continue to call me at (973) 781-3589 if you would like to discuss any aspect of our application.

Sincerely,

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

ALB/kp
Attachments

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

Tel. 973 781 7500
Fax 973 781 6325

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NDA = 91

19-Jul-2000

NDA 21-192
Lescol® (fluvastatin sodium) XL Tablets

Amendment to Pending NDA - Chemistry, Manufacturing and Controls

Noted
SC
9/7/00

FDA Center for Drug Evaluation and Research
Office of Drug Evaluation II Parklawn
5600 Fishers Lane
Rockville, Maryland 20857

Attention: John Jenkins, MD, Acting Director
Division of Metabolic and Endocrine Drug Products/HFD-510

Dear Dr. Jenkins:

At this time, Novartis is updating the referenced pending NDA with the following:

1. Updated draft labeling for
   - Lescol XL Tablet Trade Draft Label, bottle of 30's
   - Lescol XL Tablet Trade Draft Label, bottle of 100's
   - Lescol XL Tablet Sample Draft Label, bottle of 7's
   - Lescol XL Tablet Sample Draft Carton containing one bottle of 7's
2. Registration Stability Report for ——— Bottles and Bulk Storage in ——— Bags, Lescol XL ——— ablets, 80 mg, RSR6012B, 14-Jun-2000

Review

Administrative changes have been made to the draft trade labels to better align the labeling with the approved labeling for Lescol Capsules. The draft sample label and draft sample carton were inadvertently not included in the original NDA.

The attached, updated registration stability report contains ——— real time stability data on ——— batches of Lescol XL Tablets manufactured at the development site, Novartis, East Hanover, NJ and ——— real time stability data on ——— batches manufactured at the launch site, Novartis, Stein, Switzerland. The report also contains ——— stability data in the ——— bags which will be used for bulk storage to replace the ——— bags.

Lescol XL 80 mg Tablets
NDA 21-192
Updated draft labeling and updated stability report

On 17-Jul-2000, I contacted Dr. Sharon Kelly, reviewing chemist, Division of Metabolic and Endocrine Drug Products to inform her of this upcoming amendment. I also requested verification that this amendment would not have an impact on the October 8th action date. Dr. Kelly referred me to Ms. Margaret Simoneau who referred me to Mr. Bill Koch, both Regulatory Management Officers, Division of Metabolic and Endocrine Drug Products. Dr. Kelly, Ms. Simoneau and Mr. Koch concurred that this amendment would not be considered "major", therefore it would not have an impact on the October 8th action date.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue, please contact me directly at (973) 781-6929. If there are any general or Clinical related issues, please contact Adrian Birch, DRA Therapeutic Area representative at (973) 781-3589.

Sincerely,

Donna Kapples

Donna Kapples
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Attachments
Submitted in Duplicate
Desk copy: Ms. Regina Brown, New Jersey District Office, North Brunswick Resident Post – Certified Field Copy
Dr. Sharon Kelly, Division of Metabolic and Endocrine Drug Products, Chemistry Reviewer

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

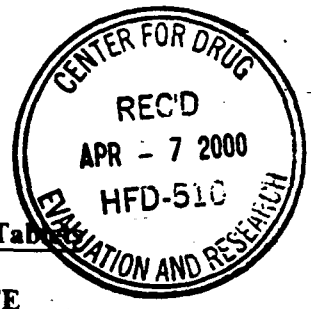
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 3590

NOVARTIS

[redacted] SU

April 6, 2000



John Jenkins, MD
Acting 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, MD 20857

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

120-DAY SAFETY UPDATE

Dear Dr. Jenkins:

We are providing you with a 120-Day Safety Update for our NDA 21-192 for Lescol® XL (fluvastatin sodium) Extended Release Tablets which is currently pending in your Division. This update consists of three primary components:

1. Pooled data analyses are provided for 747 patients, of whom 351 have completed a year or more of therapy with Lescol XL 80mg tablets by virtue of participation in studies XUO-F351-E01 and XUO-F353-E01. The year long experience for the 351 patients on Lescol XL 80 mg was obtained from 24 weeks on the F351/F353 double blind trials plus 28 weeks on the open label extensions. Those extensions have been completed, but clinical trial reports have not yet been prepared. Data listings are provided on CD-ROM for all non-efficacy parameters evaluated in those extensions.

2. Narratives have been prepared to describe and assess all SAEs that occurred in the completed studies XUO-F351E-01, XUO-F353E-01 and XUO-F356, [redacted] Additionally, narratives were prepared for patients in the completed studies who had notable ALAT/ASAT/CK abnormalities, and discontinuations due to adverse events or lab abnormalities. Narratives were also prepared for patients [redacted] who had notable ALAT/ASAT/CK abnormalities. Descriptions of the design of these studies are provided in a table of studies provided in our enclosed narrative report.

3. Case report forms are provided for all patients who experienced an SAE while participating in the completed trials XUO-F351E-01, XUO-F353E-01 and XUO-F356.

   In accordance with 21 CFR 314.90(b)(2), and consistent with past expressed preferences of representatives of your Division, all case report forms contained in this submission are only being provided on a CD-ROM. All electronic data submitted in this safety update has been virus scanned using the Network Associates VirusScan version 4.0.3a (formerly known as the McAfee VirusScan).

In the Integrated Summary of Safety provided in our original NDA, we concluded that Lescol XL 80mg Extended Release Tablets have an excellent overall tolerability profile in patients with primary hypercholesterolemia and mixed dyslipidemia. The overall adverse event profile of Lescol XL 80mg

was demonstrated to be similar to Lescol Capsules 40mg. The information contained in this safety update is supportive of our previous conclusions, and it does not necessitate any revisions to the draft labeling provided in our original submission.

If you need to discuss any aspect of this matter, please call me at (973) 781-3589.

Sincerely,

Adrian L. Birch

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

ALB/kp
Attachment
Submitted in duplicate

REVIEWS COMPLETED

CSC ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

ORIG AMENDMENT
N-BM

NOVARTIS

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

Tel 973 781 7500
Fax 973 781 3590

References

March 24, 2000

John Jenkins, MD
Acting Director
Division of Metabolic and
Endocrine Drug Products/HFD-510
Office of Drug Evaluation II
Attn: Document Control Room 14B-19
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

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

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 27 2000
HFD-510

Dear Dr. Jenkins:

Reference is made to our pending NDA No. 21-192 for Lescol® XL (fluvastatin sodium) Extended Release Tablets which is currently under review in your Division. That NDA contains data to support the approval of several indications, including one which pertains to inducing elevations of HDL-C.

We are aware that Dr. Orloff has a preference for having HDL-C data presented on the basis of the ian, 25th and 75th percentiles of the populations studied. Enclosed is a supplementary report which ses those specific parameters, and it indicates consistent findings across our three pivotal registration trials. Median percent changes ranged between +7% to +9%, the 25th percentile ranged from −1% to +2%, and the 75th percentile ranged between +12% and +17%. Lescol XL, in addition to lowering LDL-C, ApoB and triglyceride levels, also significantly increases HDL-C levels.

The data summarized in this submission were previously provided to you in SAS datasets enclosed with our original NDA which was submitted on December 8, 1999.

If any aspect of this submission requires discussion, please contact me at (973) 781-3589.

Sincerely,

Adrian L. Birch
Executive Director
Drug Regulatory Affairs

ALB/kp
Attachments
Submitted in duplicate
Desk Copies: Ms. Margaret Simoneau
Dr. David Orloff

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO ____ DATE

BEST POSSIBLE COPY

2 Page(s) Withheld

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

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

01-Mar-2000

NDA 21-192
Lescol® (fluvastatin sodium) XL Tablets

Response to FDA Question - FDA fax dated 18-Feb-2000 - Chemistry, Manufacturing and Controls

FDA Center for Drug Evaluation and Research
Office of Drug Evaluation II Parklawn
5600 Fishers Lane
Rockville, Maryland 20857

Attention: John Jenkins, MD, Acting Director
Division of Metabolic and Endocrine Drug Products/HFD-510

Dear Dr. Jenkins:

Please refer to the FDA fax sent to Novartis on 18-Feb-2000. The fax contained a request from the Biopharmaceutics reviewer to submit the detailed data sets of dissolution profiles. At this time, Novartis is providing a response to the above cited question.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue, please contact me directly at (973) 781-6929. If there are any general or Clinical related issues, please contact Adrian Birch, DRA Therapeutic Area representative at (973) 781-3589.

Sincerely,

Donna Kapples

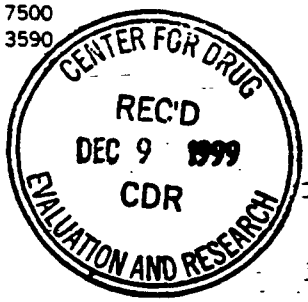
Donna Kapples
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

Attachments
Submitted in Duplicate
Desk copy: Ms. Regina Brown, New Jersey District Office, North Brunswick Resident Post – Certified Field Copy
Dr. Jim Wei, FDA Division of Biopharmaceutics
Dr. Sharon Kelly, FDA Chemistry reviewer, Division of Metabolic and Endocrine Drug Products (cover letter only)
Ms. Margaret Simoneau, FDA CSO, Division of Metabolic and Endocrine Drug Products (cover letter only)

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

Tel 973 781 7500
Fax 973 781 3590

NOVARTIS

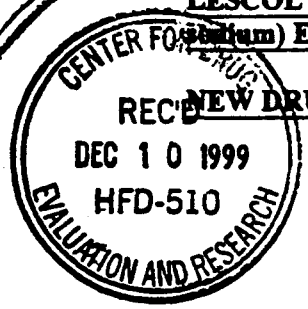


December 8, 1999

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. 21-192
LESCOL XL® (fluvastatin sodium) Extended Release Tablets

NEW DRUG APPLICATION



Dear Dr. Sobel:

In accordance with 21 CFR 314.50, Novartis Pharmaceuticals Corporation herewith submits a New Drug Application for Lescol XL® (fluvastatin sodium) Extended Release Tablets.

Lescol XL® (fluvastatin sodium) Extended Release Tablets have been studied under IND ——— which resides in your Division. The original New Drug Application for Lescol® (fluvastatin sodium) Capsules NDA 20-261 was approved on December 31, 1993. Based on data contained in that NDA and subsequent supplements, Lescol® (fluvastatin sodium) is currently indicated as an adjunct to diet in the treatment of elevated total cholesterol (Total-C), LDL-C, TG and Apo B levels in patients with primary hypercholesterolemia and mixed dyslipidemia (Frederickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate. It 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.

This New Drug Application is submitted to support the safe and effective use of Lescol XL®. In total, Lescol XL® has been administered to more than 900 patients worldwide. The data contained in this NDA demonstrate that Lescol XL® administered QPM produced highly significant median reductions in LDL-C of 35% and TG of 19% and a mean increase in HDL-C of 9% after 24 weeks of treatment in three large active controlled, double-blind randomized trials. A significantly greater reduction in LDL-C at endpoint was achieved in the Lescol XL® 80 mg QPM group (least-squares mean reduction = 32.2%) compared to the Lescol capsule 40 mg QPM group (least-squares mean reduction = 23.8%) with a least-squares mean difference of 8.4% (p value for superiority < 0.001). Additionally, the data demonstrate that the adverse event profile for Lescol XL® 80 mg is similar to the profile of Lescol® 40 mg and can be safely administered as a starting dose to patients with primary hyperlipidemia and mixed dyslipidemia.

Presented within this NDA are the results from four human pharmacokinetic and bioavailability studies (W251, W252, W253 and W351) and six controlled clinical studies (XUO-F201-E-00, XUO-F252-E-00, XUO-F253-E-00, XUO-F302-E-00, XUO-F351-E-00, and XUO-F353-E-00). Additionally, chemistry, manufacturing and controls information is provided for the Lescol XL® 80 mg extended release tablet. Consistent with agreements reached at a meeting with your Division on May 6, 1997, no additional preclinical information is necessary to support this submission. In this

regard, cross reference is made to the current New Drug Application for Lescol® (fluvastatin sodium) Capsules NDA No. 20-261 and all approved supplements for it.

With respect to pediatric labeling please be advised that Novartis has completed a study in boys where doses of Lescol® (fluvastatin sodium) capsules up to 80 mg per day were administered safely for several years. A final report and proposed pediatric labeling will be prepared for submission.

In accordance with 21 CFR 314.90(b)(2) and as agreed with representatives of your Division (teleconference of September 16, 1999), all case report forms and selected case report tabulations for this NDA which are required under 21 CFR 314.50(f) are only submitted electronically on two CD-ROMs (Volume 57). Additionally, electronic reviewers aids are being provided on a single CD-ROM (Microsoft Word files) in Volume 1 that will contain the following: draft package insert, overall summaries for the Human Pharmacokinetics and Bioavailability and Clinical Data Sections, all Clinical Pharmacology and Controlled Study report narratives and narratives for the Integrated Summaries of Safety, Efficacy and Benefits and Risks. All electronic data being submitted in this NDA has been virus scanned using the Network Associates VirusScan version 4.0.3a (Formerly known as McAfee VirusScan).

A certified copy of the Chemistry, Manufacturing and Controls Section of this New Drug Application is being provided to our district office in compliance with the pre-approval inspection (PAI) requirements.

The FDA User Fee for this application (user fee ID 3855) was submitted on December 3, 1999.

Novartis Pharmaceuticals Corporation considers the information contained in this application to be confidential, and its contents are not to be disclosed without our express written consent.

Please refer any questions or comments regarding this New Drug Application to me at 973-781-8145.

Sincerely,

Jerry Klimek

Jerry Klimek
Associate Director
Drug Regulatory Affairs