# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number: 020261/S018/S022**

**Trade Name: LESCOL CAPSULES**

**Generic Name: FLUVASTATIN SODIUM**

**Sponsor: NOVARTIS PHARMACEUTICAL CORPORATION**

**Approval Date: 03/08/99**

**Indication(s): THE REDUCTION OF TRIGLYCERIDES AND ApoB IN PATIENTS WITH PRIMARY HYPERCHOLESTEREMIA**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION: 020261/S018/S022

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| Approval Letter | X | | | |
| Tenative Approval Letter | | | | X |
| Approvable Letter | | | | X |
| Final Printed Labeling | | | | X |
| Medical Review(s) | X | | | |
| Chemistry Review(s) | X | | | |
| EA/FONSI | X | | | |
| Pharmacology Review(s) | X | | | |
| Statistical Review(s) | | | | X |
| Microbiology Review(s) | | | | X |
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| Bioequivalence Review(s) | | | | X |
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# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number: 020261/S018/S022**

## APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-261/S-018 and S-022

MAR 8 1999

Novartis Pharmaceutical Corporation
Attention: Jerry Klimek
Associate Director Regulatory Affairs
59 Route 10
East Hanover, New Jersey 07936

Dear Mr. Klimek:

Please refer to your supplemental new drug application dated July 21, 1998, received July 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lescol (fluvastatin sodium) Capsules.

We acknowledge receipt of your submissions dated December 1, 1998, and January 4 and 6, 1999.

Further administrative review has indicated that the referenced submission must be unbundled into two supplements, each of which requires clinical data for approval. The separation of the supplements is described below. A user fee for a supplement with clinical data is now due for Supplement-022.

**Supplement-018** provides for a new indication, the reduction of triglycerides and ApoB in patients with primary hypercholesterolemia and mixed dyslipidemia (INDICATIONS AND USAGE), and the supporting clinical studies are described in the CLINICAL PHARMACOLOGY section.

**Supplement-022** provides for a reduction in the recommended frequency of Liver Function Testing (LFT) and eliminates periodic, i.e., semi-annual, LFT monitoring (WARNINGS section).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted January 6, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplemental NDA 20-261/S-018 and S-022." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely yours,

/S/ 3/8/99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020261/S018/S022

## MEDICAL REVIEW(S)

**NDA# 20-261/S-018**
**Lescol (fluvastatin sodium) tablets**
**Novartis**
**Date of submission: July 21, 1998**
**Date of review: November 18, 1998**
**Supplemental NDA proposing changes to labeling: revision of "Indications and Usage" to add reduction of triglycerides and revision of "Warnings" with regard to the frequency of LFT monitoring recommended.**

**Team Leader review of NDA supplement**

**1. Lescol and triglyceride lowering**
The "Triglyceride" report is based on the pooled data on lipid altering from all Lescol placebo-controlled studies of at least 6 week duration. The total number of patients was 1752, with approximately 750 each treated with Lescol 20 and 40 mg and 257 treated with Lescol 80 mg. Data on median percent change from baseline to week 24 for lipid parameters are presented in the report. In addition, results are presented after subgrouping based on baseline TG level ($\geq$ 200 mg/dL versus < 200 mg/dL). The data support the sponsor's conclusion that the ratio of reduction in TG to that in LDL-C is independent of dose but dependent upon baseline TG, with greater TG lowering per LDL-C lowering in the patients with higher baseline TG. This is consistent with findings for other members of this class.

In summary, in patients with mixed dyslipidemia (Fredrickson Type IIb), Lescol effects clinically significant, dose-dependent reductions in triglycerides as well as TC and LDL-C. In addition, parallel reductions in Apo B are also observed.

These findings support the proposed changes in labeling with regard to the efficacy of Lescol (in **Clinical Pharmacology, Indications and Usage**).

**With regard to proposed labeling:**
**Clinical Pharmacology**
A subheading, Dyslipidemia," should be added and the first paragraph revised to include the proposed The summary statement of the effect of Lescol should read, The text need not be redundant with respect to the proposed new table to follow.

The proposed table should be called " The top subsection of the table should contain the heading Numbers of patients (N) in each treatment group should also be included.

**Indications and Usage**
The proposed changes are acceptable.

**2. Adverse hepatic effects of Lescol and LFT-monitoring recommendations in labeling**

The "LFT" report was based on pooled data from all Lescol placebo-controlled studies of at least 6 weeks duration. In addition, data from the placebo-controlled trials of duration > 12 weeks were analyzed separately.

**Significant findings**:
For any single elevation in either ALT or AST to > 3 X ULN, there is a dose-dependent increase in incidence. Rates are 1.1%, 1.1%, 2.7%, and 8.2% for placebo, 20 mg, 40 mg, and 80 mg groups, respectively. Across the dosage range, the frequency of such events falls over time, with the greatest drop after 12 weeks of therapy. It is interesting to note that the rate among placebo patients increases slightly over time. The overall incidence of single ALT or AST value > 3 X ULN was 1.1% for placebo and 3.2% for Lescol, with the exposure to Lescol weighted to the 20 and 40 mg doses.

Persistent elevations in either ALT or AST occurred in 0.2%, 0.2%, 1.9%, and 3.9% of patients taking placebo, 20, 40, and 80 mg of Lescol, respectively.

All patients who ultimately developed persistent marked transaminases elevations had either abnormal baseline transaminases or elevations noted in the first 8 weeks of treatment. Finally, all but two cases of persistent marked transaminase elevation occurred by the 12$^{th}$ week of treatment.

Taken together, these data suggest overall a low rate of clinically significant LFT abnormalities in patients treated with Lescol and that LFT monitoring out to 12 weeks after initiation of therapy or increase in dose will, on the one hand, capture virtually all cases of significant elevation, and, on the other, will reveal all the patients destined ultimately to develop clinically significant elevations in LFTs, even if they don't reach 3 X ULN until after 12 weeks of treatment. Thus, LFT checks at baseline and after 12 weeks of therapy, with instructions to follow any elevation with frequent retesting until resolved (already in all statin labels) appears to be a prudent approach to the safe use of Lescol.

**With regard to labeling:**

The above comments have been conveyed to the sponsor by telephone on 11-18-98.

**Recommendation**
Once agreement has been reached on final revised labeling, this supplemental NDA may be approved.



David G. Orloff, M.D.
Medical Team Leader
DMEDP/CDER/FDA

/S/
11-18-98

Recommendation code: AP
cc:
NDA Arch 20-261
HFD-510
HFD-510: Simoneau/Herman

Concur.
/S/
12/3/98

NOV 10 1998

NDA 20-261
Lescol (fluvastatin sodium)

October 26, 1998
Novartis Pharmaceuticals Corp.

Review and Evaluation of Clinical Data
Submission dated July 21, 1998

1 Background

1.1 Introduction

This supplement to the approved NDA for Lescol Capsules seeks approval for revisions to the current package insert regarding (i) testing that is performed in order to monitor liver function (LFT) and (ii) with respect to claims concerning alterations of level of triglycerides (TG) in those currently approved indications.

Fluvastatin is a cholesterol lowering agent (one of the class of HMGRIs or statins) that acts through the competitive inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR). HMGR itself is responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces cholesterol in hepatic cells; this in turn stimulates synthesis of LDL receptors and thereby increases the uptake of LDL particles. The end result of these biochemical processes is a reduction of cholesterol concentration in plasma.

1.2 Fluvastatin for this and other indications

Fluvastatin is currently approved as an adjunct to diet for treatment of patients with primary hypercholesterolemia and primary mixed hyperlipidemia (Fredrickson Type IIa and Type IIb). This supplement does not seek to extend the list of those specific disorders indicated for treatment by this agent, but does enlarge upon the abnormalities potentially able to be corrected by the product.

1.3 Proposed labeling related to this indication

Presently proposed labeling revises portion of Warnings that deals with liver function test monitoring requirements and adds to both the sections of Clinical Pharmacology as well as Indications and Usage new portions that provide information concerning triglyceride (TG) alterations in the approved indications.

2 Clinical Data Sources

The sponsor states that the revisions and alterations in labeling in this submission are "supported by pooled analyses of previously submitted double-blind, placebo controlled trials."

3 Clinical Study

There have been no new studies conducted for this specific submission.

A report entitled "Liver Function Test (LFT) Monitoring" is contained as substantiation for the labeling changes in Warnings. The pooled analysis presents results of all Lescol placebo-controlled studies that had a duration of at least 6 weeks and lasted up to 130 weeks. In addition, placebo-controlled studies with treatment duration of 12 weeks or longer "were separately reviewed to focus on data pertaining to the need for transaminase measurements in the 6-12 week interval after initiation of therapy." A total of 14 separate studies contributed to this database.

A report entitled "Primary Mixed Hyperlipidemia" is also included; this "discusses the results of a pooled analysis of all Lescol . . . placebo controlled studies in patients with primary combined (mixed) hyperlipidemia (Type IIb) defined as baseline triglyceride levels > 200 mg/dL."

3.1 Objective/rationale
"It is proposed, subsequent to review and analysis of databases for placebo-controlled Lescol studies, that the number of LFT measurements be reduced " from that now recommended in package insert. "It is argued that abnormalities in LFTs, if they do occur, will occur early in the initiation of therapy or after a dose increase." The sponsor claims that the risk of subsequent marked elevations of transaminase measurements in those subjects whose values are within normal range after 6-12 weeks of treatment is essentially equivalent to placebo. "Eliminating periodic transaminase measurements will avoid unnecessary and costly laboratory evaluations which cause the subject needless risk and discomfort."

The report titled "Primary Mixed Hyperlipidemia" states that most "observational studies have not found triglycerides (TG) to independently predict coronary heart disease (CHD) risk when high-density lipoprotein cholesterol (HDL-C) and other known risk factors are included in a multifactorial analysis." However, in those with elevations of low-density lipoprotein cholesterol (LDL-C), triglyceride-rich lipoproteins may independently contribute to atherosclerosis. "It is recognized that increased serum TG elicits modifications in other lipoproteins and in the coagulation system." Employment of higher doses as well as the availability of more potent HMGRIs "has led to the recognition that these agents have meaningful effects on triglycerides." Review of work with statins "suggests that these agents all have TG-reducing effects that are proportional to their LDL-C-reducing effects."

If the percentage change in TG is divided by percentage change in LDL-C, then all statins "have a similar ratio which is dependent only on the baseline TG level of the population under study." Thus, "potency and dose of use are the only meaningful differences with respect to TG reduction." When data from earlier placebo-controlled studies are examined, Lescol can be shown to have effects on TGs that are similar to atorvastatin and other statins.

3.2 Design

As stated, all trials included in this analysis were placebo-controlled and of a duration at least 6 weeks. Subjects from placebo, Lescol 20-30 mg, Lescol 40-60 mg, Lescol 80 mg, all Lescol only, and Lescol+cholestyramine groups were included for analysis. The Lescol 20 mg, Lescol 40 mg, Lescol 80 mg, and all Lescol only groups "excluded subjects on combination therapy" (eg, Lescol+cholestyramine).

3.3 Protocol

3.3.1 Population, Procedures

The trials contained for these analyses included 1030 patients treated with placebo and 1752 administered fluvastatin in various dosages. All subjects were predominantly Caucasian; mean weight and mean body mass indices were similar between the groups.

3.3.2 Endpoints

The rate of abnormalities of LFTs (SGOT/ASAT and SGPT/ALAT) that occurred in the first 6 weeks of Rx was compared to the rate of abnormalities in subsequent time intervals.

3.3.3 Statistical Methods (in addition see statistician's review)

Single occurrences of an abnormality >3 times upper limit of normal (ULN) are separated. "Persistent" abnormalities were defined as elevations >3 times ULN on 2 consecutive occasions. Abnormalities for SGOT, SGPT, and SGOT/SGPT were evaluated separately. Those subjects included in the SGOT/SGPT elevated category contained those with one or both parameters elevated at the first measurement, and the same, both, or the other parameter elevated at the second measurement. Subjects were counted once for each dose they received. Data from all exposures were included in the subsequent analysis. If there were multiple occurrences of an abnormality on a given dose, then only the earliest occurrence of that abnormality was used. Only subjects with available and "appropriate" f/u values were included in the analysis.

3.4 Results

3.4.1 Disposition/demographics

Baseline demographic information for the all placebo-controlled studies population was similar between Lescol treatment groups and the placebo group. Percentage of males ranged from 56 in Lescol 80 mg group to 63 in placebo group. All groups were predominantly Caucasian. Mean weight was similar between groups, as were mean body mass indices.

For analysis for TG effects in Primary Mixed Hyperlipidemia, all Lescol placebo-controlled studies that were of at least 6 weeks duration were included and assessed. Percentage reductions in TG and LDL-C, as well as the ratio of percentage change in TG to percentage change in LDL-C, were assessed at weeks 12 and 24 of therapy. Twelve studies were included in this database. Placebo, Lescol 20-30 mg, Lescol 40-60 mg, and Lescol 80 mg groups were included in analysis.

For the trials in primary mixed hyperlipidemia, baseline demographic information for the all placebo-controlled studies population was similar between Lescol treatment groups and the placebo group. Mean age was 53.2 and 54.7. Other usual parameters (such as weight, gender, etc) were similar between the groups.

3.4.2 Efficacy

The incidence of persistent transaminase, or LFT, elevations was greater in Lescol-treated than untreated subjects during the first 12 weeks of Rx. However, after 12 weeks therapy the number and percentage of Lescol-treated patients with persistent (as defined) elevations was small and no greater than in placebo group. Analysis of single LFT abnormalities >3 times ULN also showed "low rates of incidence" after the first 12 weeks of therapy.

"All patients who developed persistent liver enzyme abnormalities > 3 times ULN during the first 12 weeks of therapy demonstrated liver enzyme abnormalities that were detected at baseline (prior to initiation of therapy) and/or by 8 weeks after therapy with Lescol."

Review of the data from all placebo-controlled studies encompassing subjects with newly-occurring or worsening persistent liver enzyme elevations shows that the number of subjects with SGOT abnormalities for the first 12 weeks of Rx was small (6 of 1644 subjects, or 0.36%) for the All Lescol group, and decreased to 1 in 812 subjects (0.12%) after week 12. In contrast, none of the placebo subjects experienced SGOT elevations for the time periods that were analyzed. For the test of SGPT, a greater number of All Lescol subjects experienced abnormalities during the first 12 weeks Rx (18 of 1644, or 1.09%); as with the previous test, this number showed a sharp decrease after week 12 (2 of 812, or 0.25%).

The number of subjects in the SGOT/SGPT category (defined as those with one parameter elevated at the first measurement, and then the same or the other parameter increased by the second measurement) was highest for the All Lescol group during the first 12 weeks of Rx (20 of 1644 subjects, or 1.22%) with abnormalities, compared to 1 in 971 placebo subjects (0.10%). The number of All Lescol patients with such SGOT/SGPT abnormalities decreased significantly after week 12 to 2 of 812 subjects (0.25%); this was similar to the 2 of 573 placebo subjects showing an abnormality after week 12 (0.35%). Upon further review of those 20 pts in the All Lescol group who developed abnormalities during the first 12 weeks, it was revealed that 17 developed persistent liver enzyme elevations > 3 times ULN during their first 8 weeks of Rx or after dose change. Of the remaining 3, two had abnormal liver enzyme tests (but of < 3 times ULN) at baseline but developed persistent liver enzyme elevations between weeks 10 and 12 after beginning Lescol Rx. The 1 remaining pt developed persistent liver enzyme elevations at week 9 of Lescol Rx, but this subject showed abnormalities < 3 times ULN at weeks 3 and 6 after initiation of Rx.

The number of subjects at all Lescol dosages who experienced single LFT elevations > 3 times ULN was greater than the number showing persistent elevations. Time course of elevations, however, was similar, with most occurring within first 12 weeks of Rx and with a rate no greater than placebo in subsequent intervals. In the All Lescol group 48 of 1692 subjects (2.84%) experienced SGOT/SGPT abnormalities during the first 12 weeks of treatment, compared to 3 of 1023 placebo subjects (0.29%). However, after 12 weeks therapy the number of All Lescol subjects with SGOT/SGPT abnormalities decreased to 6 of 971 (0.62%), while number of placebo subjects with SGOT/SGPT abnormalities increased to 8 of 640 (1.25%).

When data from all placebo-controlled studies with treatment duration equal to or greater than 12 weeks are examined for newly-occurring or worsening persistent liver enzyme elevations, this shows that the majority of SGOT/SGPT abnormalities occurred in the first 12 weeks of treatment (14 of 1119 subjects, or 1.25%, in the All Lescol subjects compared to 1 in 666 placebo subjects, or 0.15%). The number of these dropped after 12 weeks (2 in 731 of the All Lescol subjects, or 0.27%, and 2 in 493 placebo subjects, or 0.41%).

The incidence of "single, newly-occurring or worsening" LFT elevations > 3 times ULN for all placebo-controlled studies with treatment duration 12 weeks or longer was "nearly identical" to that seen for data for all placebo-controlled studies, with a greater number of subjects receiving Lescol experiencing LFT elevations during the first 12 weeks of Rx as compared to the number seen after 12 weeks of treatment. "As with the all placebo-controlled data, incidences of LFT abnormalities were no greater in the Lescol-treated groups compared to the Placebo group after 12 weeks of therapy."

Data from all placebo-controlled studies with treatment duration 12 weeks or longer showed "a low number of subjects experiencing abnormalities after 6 weeks of treatment when they had all liver enzyme evaluations within the laboratory normal range during the first 6 weeks of treatment." Only 1 of 890 All Lescol subjects (0.11%) had a newly-occurring or worsening persistent abnormality during the study interval > 6 weeks to 12 weeks, and none showed elevations during the > 12 to 24 weeks study interval.

The following tables are relevant and are reproduced from the sponsor's submission as they occur in the reviewed volumes:

Number and Percent of Subjects with Newly-Occurring or Worsening Persistent Liver Enzyme Elevations
All Placebo-Controlled Studies

| Parameter (unit) Treatment Group | First Occurrence At Interval of: 0 - 6 Weeks n / N | % | >6 - 12 Weeks n / N | % | >12 - 24 Weeks n / N | % | >24 Weeks n / N | % |
|---|---|---|---|---|---|---|---|---|
| **SGOT (ASAT) (U/L)** | | | | | | | | |
| Placebo | 0 / 971 | 0.00 | 0 / 773 | 0.00 | 0 / 573 | 0.00 | 0 / 355 | 0.00 |
| Lescol 20 mg | 0 / 862 | 0.00 | 0 / 558 | 0.00 | 0 / 322 | 0.00 | 0 / 213 | 0.00 |
| Lescol 40 mg | 3 / 856 | 0.35 | 0 / 576 | 0.00 | 1 / 293 | 0.34 | 0 / 193 | 0.00 |
| Lescol 80 mg | 0 / 254 | 0.00 | 3 / 249 | 1.20 | 0 / 240 | 0.00 | 0 / 0 | 0.00 |
| All Lescol | 3 / 1644 | 0.18 | 3 / 1312 | 0.23 | 1 / 812 | 0.12 | 0 / 406 | 0.00 |
| Lescol + CME | 0 / 154 | 0.00 | 1 / 140 | 0.71 | 0 / 142 | 0.00 | 2 / 101 | 1.98 |
| **SGPT (ALAT) (U/L)** | | | | | | | | |
| Placebo | 1 / 971 | 0.10 | 0 / 773 | 0.00 | 1 / 573 | 0.17 | 1 / 355 | 0.28 |
| Lescol 20 mg | 1 / 862 | 0.12 | 1 / 558 | 0.18 | 0 / 322 | 0.00 | 0 / 213 | 0.00 |
| Lescol 40 mg | 8 / 856 | 0.93 | 2 / 576 | 0.35 | 1 / 293 | 0.34 | 0 / 193 | 0.00 |
| Lescol 80 mg | 1 / 254 | 0.39 | 5 / 249 | 2.01 | 1 / 240 | 0.42 | 0 / 0 | 0.00 |
| All Lescol | 10 / 1644 | 0.61 | 8 / 1312 | 0.61 | 2 / 812 | 0.25 | 0 / 406 | 0.00 |
| Lescol + CME | 0 / 154 | 0.00 | 1 / 140 | 0.71 | 1 / 142 | 0.70 | 2 / 101 | 1.98 |
| **SGOT (ASAT) / SGPT (ALAT) (U/L)** | | | | | | | | |
| Placebo | 1 / 971 | 0.10 | 0 / 773 | 0.00 | 1 / 573 | 0.17 | 1 / 355 | 0.28 |
| Lescol 20 mg | 1 / 862 | 0.12 | 1 / 558 | 0.18 | 0 / 322 | 0.00 | 0 / 213 | 0.00 |
| Lescol 40 mg | 10 / 856 | 1.17 | 2 / 576 | 0.35 | 1 / 293 | 0.34 | 0 / 193 | 0.00 |
| Lescol 80 mg | 1 / 254 | 0.39 | 5 / 249 | 2.01 | 1 / 240 | 0.42 | 0 / 0 | 0.00 |
| All Lescol | 12 / 1644 | 0.73 | 8 / 1312 | 0.61 | 2 / 812 | 0.25 | 0 / 406 | 0.00 |
| Lescol + CME | 0 / 154 | 0.00 | 1 / 140 | 0.71 | 1 / 142 | 0.70 | 3 / 101 | 2.97 |

Persistent Abnormality: Newly-occurring or worsening and > 3*ULN on two consecutive occasions.

Source: pbolft.sas

Number and Percent of Subjects with Newly-Occurring or Worsening Liver Enzyme Elevations
Single Value Greater Than 3 Times Upper Limit of Normal
All Placebo-Controlled Studies

| Parameter (unit) Treatment Group | First Occurrence At Interval of: 0 - 6 Weeks n / N | % | >6 - 12 Weeks n / N | % | >12 - 24 Weeks n / N | % | >24 Weeks n / N | % |
|---|---|---|---|---|---|---|---|---|
| **SGOT (ASAT) (U/L)** | | | | | | | | |
| Placebo | 1 / 1023 | 0.10 | 0 / 844 | 0.00 | 3 / 640 | 0.47 | 2 / 528 | 0.38 |
| Lescol 20 mg | 3 / 866 | 0.35 | 0 / 628 | 0.00 | 0 / 384 | 0.00 | 0 / 217 | 0.00 |
| Lescol 40 mg | 9 / 901 | 1.00 | 3 / 605 | 0.50 | 1 / 387 | 0.26 | 0 / 281 | 0.00 |
| Lescol 80 mg | 3 / 257 | 1.17 | 4 / 255 | 1.57 | 0 / 243 | 0.00 | 0 / 1 | 0.00 |
| All Lescol | 15 / 1692 | 0.89 | 7 / 1416 | 0.49 | 1 / 971 | 0.10 | 0 / 499 | 0.00 |
| Lescol + CME | 0 / 156 | 0.00 | 1 / 141 | 0.71 | 2 / 149 | 1.34 | 2 / 107 | 1.87 |
| **SGPT (ALAT) (U/L)** | | | | | | | | |
| Placebo | 1 / 1023 | 0.10 | 2 / 844 | 0.24 | 4 / 640 | 0.63 | 4 / 528 | 0.76 |
| Lescol 20 mg | 4 / 866 | 0.46 | 3 / 628 | 0.48 | 2 / 384 | 0.52 | 0 / 217 | 0.00 |
| Lescol 40 mg | 15 / 901 | 1.66 | 4 / 605 | 0.66 | 1 / 387 | 0.26 | 1 / 281 | 0.36 |
| Lescol 80 mg | 11 / 257 | 4.28 | 8 / 255 | 3.14 | 2 / 243 | 0.82 | 0 / 1 | 0.00 |
| All Lescol | 29 / 1692 | 1.71 | 15 / 1416 | 1.06 | 5 / 971 | 0.51 | 1 / 499 | 0.20 |
| Lescol + CME | 0 / 156 | 0.00 | 1 / 141 | 0.71 | 3 / 149 | 2.01 | 1 / 107 | 0.93 |
| **SGOT (ASAT) / SGPT (ALAT) (U/L)** | | | | | | | | |
| Placebo | 1 / 1023 | 0.10 | 2 / 844 | 0.24 | 4 / 640 | 0.63 | 4 / 528 | 0.76 |
| Lescol 20 mg | 5 / 866 | 0.58 | 3 / 628 | 0.48 | 2 / 384 | 0.52 | 0 / 217 | 0.00 |
| Lescol 40 mg | 16 / 901 | 1.78 | 6 / 605 | 0.99 | 1 / 387 | 0.26 | 1 / 281 | 0.36 |
| Lescol 80 mg | 11 / 257 | 4.28 | 8 / 255 | 3.14 | 2 / 243 | 0.82 | 0 / 1 | 0.00 |
| All Lescol | 31 / 1692 | 1.83 | 17 / 1416 | 1.20 | 5 / 971 | 0.51 | 1 / 499 | 0.20 |
| Lescol + CME | 0 / 156 | 0.00 | 1 / 141 | 0.71 | 3 / 149 | 2.01 | 2 / 107 | 1.87 |

Source: sbolft1.sas

Data for reduction in TG and LDL-C values "showed increasing efficacy with increasing dose. Reductions in TG were also dependent on baseline TG levels." There was, however, a fixed ratio of TG to LDL-C reduction that was dependent only on baseline TG level. "TG reductions with HMGRIs are generally proportional to LDL-C reductions with a factor depending on baseline TG values." Reductions in TG, it is said, tend to be small when baseline TG is <150 mg/dL. When baseline TG >250 mg/dL, then TG reductions tend to be much greater, and the ratio of percentage change in TG/LDL-C approaches 1.0.

In the analysis performed for this sNDA, ratios of TG/LDL-C for those Lescol-treated subjects who had baseline TG > or = 200 mg/dL were nearly twice those seen for those subjects with baseline TG < 200 mg/dL. In addition to the decreases found for TG and LDL-C, there were modest increases in HDL-C found for all Lescol treatment groups; these results "appeared dependent on baseline triglyceride levels as well as dose." All of the Lescol treatment groups also showed decreases in apo B; although this change was dose-dependent, baseline TG values did not appear to have an effect on magnitude of change in this parameter.

The following table again is reproduced from the sponsor's submission of data and analysis as contained in the reviewed volumes:



Text Table 2 Percent Change in Lipid Parameters from Baseline to Week 24
All Placebo-Controlled Studies

| | Median | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | TG | | LDL-C | | HDL-C | | Apo B | |
| Dose | n | %Δ | n | %Δ | n | %Δ | n | %Δ |
| **All Subjects** | | | | | | | | |
| Lescol 20 mg | 747 | -11.88 | 747 | -22.22 | 747 | 3.30 | 114 | -19.28 |
| Lescol 40 mg | 748 | -13.51 | 748 | -24.97 | 748 | 4.35 | 125 | -18.34 |
| Lescol 80 mg | 257 | -17.76 | 257 | -35.88 | 257 | 5.56 | 232 | -28.43 |
| All Lescol | 1752 | -13.29 | 1752 | -24.85 | 1752 | 4.07 | 471 | -23.79 |
| **Baseline TG <200 mg/dL** | | | | | | | | |
| Lescol 20 mg | 599 | -10.78 | 599 | -22.52 | 599 | 2.80 | 91 | -19.33 |
| Lescol 40 mg | 569 | -11.76 | 569 | -25.42 | 569 | 3.30 | 75 | -18.37 |
| Lescol 80 mg | 181 | -12.68 | 181 | -36.41 | 181 | 4.55 | 163 | -28.43 |
| All Lescol | 1349 | -11.53 | 1349 | -25.06 | 1349 | 3.30 | 332 | -23.77 |
| **Baseline TG ≥200 mg/dL** | | | | | | | | |
| Lescol 20 mg | 148 | -17.25 | 148 | -21.63 | 148 | 5.81 | 23 | -19.23 |
| Lescol 40 mg | 179 | -19.62 | 179 | -23.51 | 179 | 6.85 | 47 | -18.34 |
| Lescol 80 mg | 76 | -23.18 | 76 | -34.55 | 76 | 8.95 | 69 | -28.13 |
| All Lescol | 403 | -19.78 | 403 | -23.83 | 403 | 6.85 | 139 | -23.90 |

4 Safety Review

4.1 Exposure

One of the two chief purposes of this submission is to alter the recommendations for timing for liver function testing. As such, discussion of this aspect is contained above under the "efficacy" heading. No other aspects of safety are involved, analyzed, or impinged upon.

4.2 Demographics

See the discussion above under aspects of "efficacy."

4.3 Disposition

4.4 Adverse Events

4.4.1 Clinical Events

See above discussion and summary.

APPEARS THIS WAY
ON ORIGINAL

4.4.2 Clinical Labs

No new lab tests were performed for this submission. The supplement consists of a re-analysis of previously gathered data.

4.5 Conclusions regarding safety

The only aspect regarding safety in this submission relates to timing and frequency of performance of tests to assess liver function. All general conclusions regarding toxicities and organ involvement by this drug remain unchanged.

5 Labeling in toto (and by section if relevant)

The package insert is modified to add a table to show median percentage changes in lipid parameters (total-C, TG, LDL-C, apo-B, and HDL-C) from baseline to week 24 endpoint. The table below is reproduced from the sponsor's submission:

**All Patients Median Percent Change in Lipid Parameters from Baseline to Week 24 Endpoint All Placebo-Controlled Studies**

| Dose | Total-C %Δ | TG %Δ | LDL-C %Δ | Apo B %Δ | HDL-C %Δ |
|---|---|---|---|---|---|
| Lescol 20 mg | -16.6 | -11.9 | -22.2 | -19.3 | +3.3 |
| Lescol 40 mg | -18.6 | -13.5 | -25.0 | -18.3 | +4.4 |
| Lescol 80 mg | -27.0 | -17.8 | -35.9 | -28.4 | +5.6 |
| Baseline TG ≥200 mg/dL | | | | | |
| Lescol 20 mg | -16.4 | -13 | -21.6 | -19.2 | +5.8 |
| Lescol 40 mg | -17.8 | -19.6 | -23.5 | -18.3 | +6.9 |
| Lescol 80 mg | -26.8 | -23.2 | -34.6 | -28.1 | +9.0 |

6 Conclusions

The sponsor concludes from the LFT survey that the percentage of subjects with persistent transaminase elevations to the degree > 3 times ULN while on Lescol was "small and similar to placebo" after 12 weeks therapy. Pts who did develop persistent liver enzyme abnormalities had "detectable" liver enzyme abnormalities at baseline and/or by 8 weeks Rx with Lescol. "This suggests that measurements of SGOT/SGPT can be made at baseline (prior to the initiation of therapy) and at 8 weeks of treatment or change in dose to assess the risk of future abnormalities." The pharmaceutical firm claims that "further monitoring of transaminase levels is not necessary in subjects with values found to be in the normal range. Subjects with detected abnormal transaminase levels or signs and symptoms of liver disease should be monitored to confirm abnormal values and be followed therafter [sic] with frequent liver function tests until the abnormality (ies) return to normal. Should an increase in AST or ALT remain > 3 times ULN persistently (found on two consecutive occassions [sic]), it is recommended to withdraw therapy with fluvastatin sodium."

The company concludes that the ratio {reduction in TG/reduction in LDL-C} is "similar between Lescol and other statins, including atorvastatin." Similarly to the other statins, "this proportional decrease is not dependent on dose but on baseline triglyceride values"; those who exhibit baseline hypertriglyceridemia experience the greatest TG to LDL-C reductions. Therefore, in subjects "with mixed dyslipidemia (Type IIb), Lescol is an effective agent for reducing TG, LDL-C, and Apo B, and for increasing HDL-C levels."

7 Recommendations

(1) Because so much of this submission depends upon statistical procedures employed in analysis of results, combining of results, etc, this submission must be independently analyzed by statisticians here in FDA.
(2) If statistical support staff have no disagreements with both methods as well as conclusions reached by the sponsor of this NDA and supplement, then this submission may be accepted and approved under the proposed draft labeling with no further modifications.

/S/

Elton Herman



A more complete review of labeling based on discussion with the Team Leader will be needed for future reviews.

/S/ 11-10-98

cc: Orig NDA 20-261 Lescol
HFD-510
HFD-510/EHerman/10-26-98

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020261/S018/S022

## CHEMISTRY REVIEW(S)

DEC 22 [illegible]

SIMONEK4

| CHEMISTS REVIEW | 1. ORGANIZATION | 2. NDA NUMBER |
|---|---|---|
| | DMEDP II, HFD-510 | 20-261 |
| 3. NAME AND ADDRESS OF APPLICANT | | 4. SUPPLEMENT NUMBER, DATE |
| Novartis Pharmaceuticals | | 21-JUL-1998 |
| 5. PROPRIETARY NAME | 6. NAME OF THE DRUG | 7. AMENDMENTS, REPORT, DATE |
| Lescol | Fluvastatin Sodium | ~~1-DEC-1998~~ 21-JUL-1998 |

8. SUPPLEMENT PROVIDES FOR

Labeling changes to the Clinical Pharmacology, Indications and Usage, and Warnings sections of the package insert.

| 9. PHARMACOLOGICAL CATEGORY | 10. HOW DISPENSED | 11. RELATED IND, NDA, DMF |
|---|---|---|
| antihypercholestremic | RX | 1-DEC-1998 |
| 12. DOSAGE FORM | 13. POTENCY | |
| Capsules, oral | 20, 40 mg | |
| 14. CHEMICAL NAME AND STRUCTURE | | |
| See Chemistry Review #1 | | |

15. COMMENTS

The sponsor has made acceptable changes to the package insert. The changes to the indications and usage section are, primarily, the inclusion of "TG and Apo B" levels in addition to total-C and LDL-C, as well as adding "mixed hyperlipidemia (Frederickson" in addition to primary hypercholesterolemia. These changes were noted in earlier studies, and were not originally considered significant. Additionally, the sponsor has requested a waiver from the requirement to prepare and EA under 21 CFR 25.21(a), certifying that approval of this labeling change will not be expected to increase the dose, duration or frequency, nor the use of the active moiety, fluvastatin sodium. This request is acceptable.

16. CONCLUSION AND RECOMMENDATION

The labeling changes are acceptable from a chemistry standpoint. The request for a waiver of the requirement to prepare an EA in support of this application is also acceptable. This application may be approved based on chemistry issues.

| 17. NAME | 18. REVIEWERS SIGNATURE | 19. DATE COMPLETED |
|---|---|---|
| WILLIAM K. BERLIN | /S/ | 21-DEC-1998 |

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/S/

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