CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-261/S019

Trade Name: Lescol Capsules

Generic Name: fluvastatin sodium

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: January 4, 1999

Indications: .

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-261/S019

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-261/S019

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-261/S-019

JAN 4 1999

Novartis Pharmaceuticals 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 August 4, 1998, received August 10, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lescol (fluvastatin).

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides for changes in the PRECAUTIONS/Drug Interactions section of the Lescol package insert. This change is the deletion of the subsection "Other Concomitant Therapy". Your submission stated September 1, 1998, as the implementation date for the change.

We have completed the review of this supplemental application and it is approved. Accordingly, the supplemental application is approved effective on the date of this letter.

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) 827-6430.

Sincerely,

1-4-99

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

cc:
Archival NDA 20-261
HFD-510/Div. Files
HFD-510/M. Simoneau
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-102/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-95/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: Mas/September 1, 1998
Initialed
by:SShen1.4.99/DOrloff1.4.99/HAhn11.24.98/WBerlin11.25.98/SMoore11.24.98/RSteigerwalt11.30
.98/E.Galliers12.31.98
final:Mas1.4.99
filename: 20261.19

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-261/S019

LABELING

C98-27 (Rev. 6/98)
666800
30753908

NOVARTIS

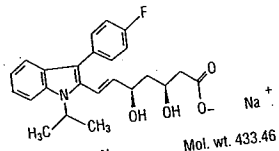
Lescol®
(fluvastatin sodium)
Capsules

Rx only

DESCRIPTION

Lescol® (fluvastatin sodium) is a water soluble cholesterol lowering agent which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase.

Fluvastatin sodium is [*R**,*S**-(*E*)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1*H*-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, monosodium salt. The structural formula is:



$C_{24}H_{25}FNO_4 \cdot Na$ Mol. wt. 433.46

This molecular entity is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. Lescol® (fluvastatin sodium) is supplied as capsules containing fluvastatin sodium, equivalent to 20 mg or 40 mg of fluvastatin, for oral administration.

Active Ingredient: fluvastatin sodium

Inactive Ingredients: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch, red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, yellow iron oxide, and other ingredients.

May Also Include: benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide and sodium propionate.

CLINICAL PHARMACOLOGY

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), and apolipoprotein B (a membrane transport complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-cholesterol (HDL-C) and its transport complex, apolipoprotein A, are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of Total-C and LDL-C and inversely with the level of HDL-C.

In patients with hypercholesterolemia, treatment with Lescol® (fluvastatin sodium) reduced Total-C, LDL-C, and apolipoprotein B. Lescol® (fluvastatin sodium) also moderately reduced triglycerides (TG) while producing an increase in HDL-C of variable magnitude. The agent had no consistent effect on either Lp(a) or fibrinogen. The effect of Lescol® (fluvastatin sodium)-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been determined.

Mechanism of Action

Lescol® (fluvastatin sodium) is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The end result of these biochemical processes is a reduction of the plasma cholesterol concentration.

Pharmacokinetics/Metabolism

Oral Absorption

Fluvastatin is absorbed rapidly and completely following oral administration, with peak concentrations reached in less than 1 hour. Following administration of a 10 mg dose, the absolute bioavailability is 24% (range 9%-50%). Administration with food reduces the rate but not the extent of absorption. At steady-state, administration of fluvastatin with the evening meal results in a two-fold decrease in C_{max} and more than two-fold increase in t_{max} as compared to administration 4 hours after the evening meal. No significant difference in extent of absorption or in the lipid-lowering effects were observed between the two administrations. After single or multiple doses above 20 mg, fluvastatin exhibits saturable first-pass metabolism resulting in higher-than-expected plasma fluvastatin concentrations. The inactive enantiomer accounts for about 60% of the increase.

Distribution

Fluvastatin is 98% bound to plasma proteins. The mean volume of distribution (VD_{ss}) is estimated at 34.4 liters. The parent drug is targeted to the liver and no active metabolites are present systemically.

Metabolism

Fluvastatin is metabolized in the liver, primarily via hydroxylation of the indole ring at the 5- and 6-positions. N-dealkylation and beta-oxidation of the side-chain also occurs. The hydroxy metabolites have some pharmacologic activity, but do not circulate in the blood. Both enantiomers of fluvastatin are metabolized in a similar manner.

Elimination

Fluvastatin is primarily (about 90%) eliminated in the feces as metabolites, with less than 2% present as unchanged drug.

Special Populations

Renal Insufficiency: No significant (<6%) renal excretion of fluvastatin occurs in humans.

Hepatic Insufficiency: Fluvastatin is subject to saturable first-pass metabolism/sequestration by the liver and is eliminated primarily via the biliary route. Therefore, the potential exists for drug accumulation in patients with hepatic insufficiency. Caution should therefore be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see WARNINGS)*.

Age: Plasma levels of fluvastatin are not affected by age.

Gender: Women tend to have slightly higher (but statistically insignificant) fluvastatin concentrations than men. This is most likely due to body weight differences, as adjusting for body weight decreases the magnitude of the differences seen.

Pediatric: No data are available. Fluvastatin is not indicated for use in the pediatric population.

Steady-state plasma concentrations show no evidence of accumulation of fluvastatin following administration of up to 80 mg daily, as evidenced by a beta-elimination half-life of less than 3 hours. However, under conditions of maximum rate of absorption (i.e., fasting) systemic exposure to fluvastatin is increased 33% to 53% compared to a single 20 mg or 40 mg dose.

Single-dose and steady-state pharmacokinetic parameters in 33 subjects with hypercholesterolemia are summarized below:

	C_{max} (ng/mL) mean±SD (range)	AUC (ng·h/mL) mean±SD (range)	t_{max} (hr) mean±SD (range)	CL/F (L/hr) mean±SD (range)	$t_{1/2}$ (hr) mean±SD (range)
20 mg single dose (n=17)	166±106 (48.9-517)	207±65 (111-288)	0.9±0.4 (0.5-2.0)	107±38.1 (69.5-181)	2.5±1.7 (0.5-6.6)
20 mg b.i.d. (n=17)	200±86 (71.8-366)	275±111 (91.6-467)	1.2±0.9 (0.5-4.0)	87.8±45 (42.8-218)	2.8±1.7 (0.9-6.0)
40 mg single dose (n=16)	273±189 (72.8-812)	456±259 (207-1221)	1.2±0.7 (0.75-3.0)	108±44.7 (32.8-193)	2.7±1.3 (0.8-5.9)
40 mg b.i.d. (n=16)	432±236 (119-990)	697±275 (359-1559)	1.2±0.6 (0.5-2.5)	64.2±21.1 (25.7-111)	2.7±1.3 (0.7-5.0)

Clinical Studies

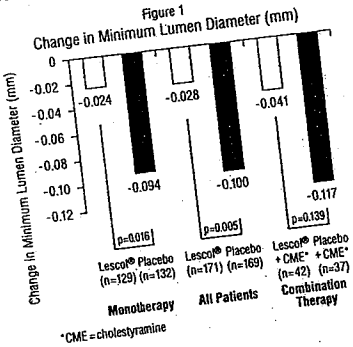
Lescol® (fluvastatin sodium) has been studied in 19 controlled studies worldwide for patients with Type IIa or IIb hyperlipoproteinemia. Lescol® (fluvastatin sodium) alone was administered to 2326 patients in daily dose regimens of 20 mg, 40 mg, and 80 mg (40 mg b.i.d.) in trials from 6-36 weeks in duration. In the largest single randomized study with Lescol® (fluvastatin sodium) (n=292), treatment at a dose of 20 mg QPM resulted in a highly significant decrease in LDL-C of 22% after nine weeks of study. In the largest single study (n=210) of patients randomized to 40 mg daily and limited to FH patients, a mean LDL-C reduction of 24% was observed. This effect was observed after 4 weeks of treatment and was maintained during the additional 8 weeks of fluvastatin administration. In the largest single controlled study (N=266) of patients randomized to 80 mg (40 mg b.i.d.) daily, a mean LDL-C reduction of 35% was observed during the initial evaluation period (average of 4 and 8 weeks exposure) and a mean LDL-C reduction of 32% was observed at endpoint (28 weeks exposure). In a long term open-label free titration study, after 96 weeks LDL-C decreases of 25% (20 mg, N=68), 31% (40 mg, N=298), and 34% (80 mg, N=209) were observed. Reductions in Apo B were also seen as a result of treatment with Lescol® (fluvastatin sodium). Small but statistically significant increases in HDL-C and corresponding decreases in TG were also noted. No consistent effect on Lp(a) was found.

Atherosclerosis

In the Lipoprotein and Coronary Atherosclerosis Study (LCAS), the effect of Lescol® (fluvastatin sodium) therapy on coronary atherosclerosis was assessed by quantitative coronary angiography (QCA) in patients with coronary artery disease and mild to moderate hypercholesterolemia (baseline LDL-C range 115-190 mg/dL). In this randomized double-blind, placebo controlled trial, 429 patients were treated with conventional measures (Step 1 AHA Diet) and either Lescol® (fluvastatin sodium) 40 mg/day or placebo. In order to provide treatment to patients receiving placebo with LDL-C levels ≥160 mg/dL at baseline, adjunctive therapy with cholestyramine was added after week 12 to all patients in the study with baseline LDL-C values of ≥160 mg/dL. These baseline levels were present in 25% of the study population. Quantitative coronary angiograms were evaluated at baseline and 2.5 years in 340 (79%) angiographic evaluable patients.

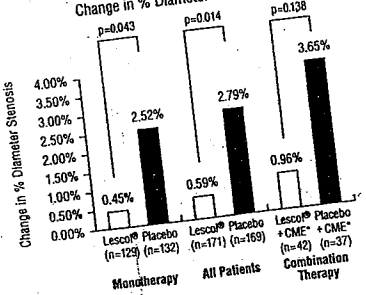
Lescol® (fluvastatin sodium) significantly slowed the progression of coronary atherosclerosis. Compared to placebo, Lescol® (fluvastatin sodium) significantly slowed the progression of lesions as measured by within-patient per-lesion change in minimum lumen diameter (MLD), the primary endpoint (see Figure 1 below), percent diameter stenosis (Figure 2), and the formation of new lesions (13% of all fluvastatin patients versus 22% of all placebo patients). Additionally, a significant difference in favor of Lescol® (fluvastatin sodium) was found between all fluvastatin and all placebo patients in the distribution among the three categories of definite progression, definite regression, and mixed or no change. Beneficial angiographic results (change in MLD) were independent of patients' gender and consistent across a range of baseline LDL-C levels.

Figure 1
Change in Minimum Lumen Diameter (mm)



*CME = cholestyramine

Figure 2
Change in % Diameter Stenosis



*CME = cholestyramine

INDICATIONS AND USAGE

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerosis vascular disease due to hypercholesterolemia. Lescol® (fluvastatin sodium) is indicated as an adjunct to diet in the treatment of elevated total cholesterol (Total-C) and LDL-C levels in patients with primary hypercholesterolemia (Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures has not been adequate.

Lescol® (fluvastatin sodium) 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.

Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other medication, or alcoholism, have been excluded. Prior to initiation of fluvastatin sodium, a lipid profile should be performed to measure Total-C, HDL-C and TG. For patients with TG <400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

$$\text{LDL-C} = \text{Total-C} - \text{HDL-C} - 1/5\ \text{TG}$$

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients LDL-C may be low or normal despite elevated Total-C. In such cases, Lescol® (fluvastatin sodium) is not indicated.

Lipid determinations should be performed at intervals of no less than 4 weeks and dosage adjusted according to the patient's response to therapy.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

LDL-Cholesterol		mg/dL (mmol/L)	
Definite Atherosclerotic Disease*	Two or More Other Risk Factors**	Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130 (≥3.4)	≤100 (≤2.6)

* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

** Other risk factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that the LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the Total-C be used to monitor therapy.

Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations	
		Major	Minor
I (rare)	Chylomicrons	TG	↑ → C
IIa	LDL	C	–
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	–
IV	VLDL	TG	↑ → C
V (rare)	Chylomicrons, VLDL	TG	↑ → C

C = cholesterol, TG = triglycerides, LDL = low density lipoprotein, VLDL = very low density lipoprotein, IDL = intermediate density lipoprotein

Lescol® (fluvastatin sodium) has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e., hyperlipoproteinemia Types I, III, IV, or V).

CONTRAINDICATIONS

Hypersensitivity to any component of this medication. Lescol® (fluvastatin sodium) is contraindicated in patients with active liver disease or unexplained, persistent elevations in serum transaminases *(see WARNINGS).*

Pregnancy and Lactation

Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Fluvastatin sodium should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes

Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. A small number of patients treated with Lescol® (fluvastatin sodium) in worldwide controlled trials (N=25, 1.1%) developed dose-related, persistent elevations of transaminase levels to more than 3 times the upper limit of normal. Fourteen of these patients (0.6%) were discontinued from therapy. In all clinical trials, a total of 33/2969 patients (1.1%) had persistent transaminase elevations with an average fluvastatin exposure of approximately 71.2 weeks; 19 of these patients (0.6%) were discontinued. The majority of patients with these abnormal biochemical findings were asymptomatic.

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter (e.g., semiannually). Liver enzyme changes generally occur in the first 3 months of treatment with Lescol® (fluvastatin sodium). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of fluvastatin sodium therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of Lescol® (fluvastatin sodium) *(see CONTRAINDICATIONS).* Caution should be exercised when fluvastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion *(see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism).* Such patients should be closely monitored.

Skeletal Muscle

Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with fluvastatin and with other drugs in this class. Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal, has been reported rarely.

Myopathy should be considered in any patients with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Fluvastatin sodium therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Fluvastatin sodium therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.

The risk of myopathy and or rhabdomyolysis during treatment with HMG-CoA reductase inhibitors has been reported to be increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. Myopathy was not observed in a clinical trial in 74 patients involving patients who were treated with fluvastatin sodium together with niacin.

Uncomplicated myalgia has been observed infrequently in patients treated with Lescol® (fluvastatin sodium) at rates indistinguishable from placebo.

The use of fibrates alone may occasionally be associated with myopathy. The combined use of HMG-CoA reductase inhibitors and fibrates should generally be avoided.

PRECAUTIONS

General

Before instituting therapy with Lescol® (fluvastatin sodium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems *(see INDICATIONS AND USAGE).*

The HMG-CoA reductase inhibitors may cause elevation of creatine phosphokinase and transaminase levels *(see WARNINGS and ADVERSE REACTIONS).* This should be considered in the differential diagnosis of chest pain in a patient on therapy with fluvastatin sodium.

Homozygous Familial Hypercholesterolemia

HMG-CoA reductase inhibitors are reported to be less effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Women should be informed that if they become pregnant while receiving Lescol® (fluvastatin sodium) the drug should be discontinued immediately to avoid possible harmful effects on a developing fetus from a relative deficit of cholesterol and biological products derived from cholesterol. In addition, Lescol® (fluvastatin sodium) should not be taken during nursing. *(See CONTRAINDICATIONS)*

Drug Interactions

Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: *See WARNINGS: Skeletal Muscle.*

Antipyrine: Administration of fluvastatin sodium does not influence the metabolism and excretion of antipyrine, either by induction or inhibition. Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system; therefore, interactions with other drugs metabolized by this mechanism are not expected.

Niacin/Propranolol: Concomitant administration of fluvastatin sodium with niacin or propranolol has no effect on the bioavailability of fluvastatin sodium.

Cholestyramine: Administration of fluvastatin sodium concomitantly with, or up to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for AUC and 50%-80% for C_{max}. However, administration of fluvastatin sodium 4 hours after cholestyramine resulted in a clinically significant additive effect compared with that achieved with either component drug.

Digoxin: In a crossover study involving 18 patients chronically receiving digoxin, a single 40 mg dose of fluvastatin had no effect on digoxin AUC, but had an 11% increase in digoxin C_{max} and small increase in digoxin urinary clearance. Patients taking digoxin should be monitored appropriately when fluvastatin therapy is initiated.

Cimetidine/Ranitidine/Omeprazole: Concomitant administration of fluvastatin sodium with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin C_{max} (43%, 70% and 50%, respectively) and AUC (24%-33%), with an 18%-23% decrease in plasma clearance.

Rifampicin: Administration of fluvastatin sodium to subjects pretreated with rifampicin results in significant reduction in C_{max} (59%) and AUC (51%), with a large increase (95%) in plasma clearance.

Warfarin: *In vitro* protein binding studies demonstrated no interaction at therapeutic concentrations. Concomitant administration of a single dose of warfarin (30 mg) in young healthy males receiving fluvastatin sodium (40 mg/day × 8 days) resulted in no elevation of racemic warfarin concentration. There was also no effect on prothrombin complex activity when compared to concomitant administration of placebo and warfarin. However, bleeding and/or increased prothrombin times have been reported in patients taking coumarin anticoagulants concomitantly with other HMG-CoA reductase inhibitors. Therefore, patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when fluvastatin sodium is initiated or the dosage of fluvastatin sodium is changed.

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

Fluvastatin exhibited no effect upon non-stimulated cortisol levels and demonstrated no effect upon thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred, suggesting that the observation was not due to a direct effect upon testosterone production. No effect upon FSH in males was noted. Due to the limited number of premenopausal females studied to date, no conclusions regarding the effect of fluvastatin upon female sex hormones may be made.

Two clinical studies in patients receiving fluvastatin at doses up to 80 mg daily for periods of 24 to 28 weeks demonstrated no effect of treatment upon the adrenal response to ACTH stimulation. A clinical study evaluated the effect of fluvastatin at doses up to 80 mg daily for 28 weeks upon the gonadal response to HCG stimulation. Although the mean total testosterone response was significantly reduced ($p<0.05$) relative to baseline in the 80 mg group, it was not significant in comparison to the changes noted in groups receiving either 40 mg of fluvastatin or placebo.

Patients treated with fluvastatin sodium who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g., ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones.

CNS Toxicity

CNS effects, as evidenced by decreased activity, ataxia, loss of righting reflex, and ptosis were seen in the following animal studies: the 18-month mouse carcinogenicity study at 50 mg/kg/day, the 6-month

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dog study at 36 mg/kg/day, the 6-month hamster study at 40 mg/kg/day, and in acute, high-dose studies in rats and hamsters (50 mg/kg), rabbits (300 mg/kg) and mice (1500 mg/kg). CNS toxicity in the acute high-dose studies was characterized (in mice) by conspicuous vacuolation in the ventral white columns of the spinal cord at a dose of 5000 mg/kg and (in rat) by edema with separation of myelinated fibers of the ventral spinal tracts and sciatic nerve at a dose of 1500 mg/kg. CNS toxicity, characterized by periaxonal vacuolation, was observed in the medulla of dogs that died after treatment for 5 weeks with 48 mg/kg/day; this finding was not observed in the remaining dogs when the dose level was lowered to 36 mg/kg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. No CNS lesions have been observed after chronic treatment for up to 2 years with fluvastatin in the mouse (at doses up to 350 mg/kg/day), rat (up to 24 mg/kg/day), or dog (up to 16 mg/kg/day).

Prominent bilateral posterior Y suture lines in the ocular lens were seen in dogs after treatment with 1, 8, and 16 mg/kg/day for 2 years.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year study was performed in rats at dose levels of 6, 9, and 18-24 (escalated after 1 year) mg/kg/day. These treatment levels represented plasma drug levels of approximately 9, 13, and 26-35 times the mean human plasma drug concentration after a 40 mg oral dose. A low incidence of forestomach squamous papillomas and 1 carcinoma of the forestomach at the 24 mg/kg/day dose level was considered to reflect the prolonged hyperplasia induced by direct contact exposure to fluvastatin sodium rather than to a systemic effect of the drug. In addition, an increased incidence of thyroid follicular cell adenomas and carcinomas was recorded for males treated with 18-24 mg/kg/day. The increased incidence of thyroid follicular cell neoplasm in male rats with fluvastatin sodium appears to be consistent with findings from other HMG-CoA reductase inhibitors. In contrast to other HMG-CoA reductase inhibitors, no hepatic adenomas or carcinomas were observed.

The carcinogenicity study conducted in mice at dose levels of 0.3, 15 and 30 mg/kg/day revealed, as in rats, a statistically significant increase in forestomach squamous cell papillomas in males and females at 30 mg/kg/day and in females at 15 mg/kg/day. These treatment levels represented plasma drug levels of approximately 0.05, 2, and 7 times the mean human plasma drug concentration after a 40 mg oral dose.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; malignant transformation assay in BALB/3T3 cells; unscheduled DNA synthesis in rat primary hepatocytes; chromosomal aberrations in V79 Chinese Hamster cells; HGPRT V79 Chinese Hamster cells. In addition, there was no evidence of mutagenicity *in vivo* in either a rat or mouse micronucleus test.

In a study in rats at dose levels for females of 0.6, 2 and 6 mg/kg/day and at dose levels for males of 2, 10 and 20 mg/kg/day, fluvastatin sodium had no adverse effects on the fertility or reproductive performance.

Seminal vesicles and testes were small in hamsters treated for 3 months at 20 mg/kg/day (approximately three times the 40 milligram human daily dose based on surface area, mg/m²). There was tubular degeneration and aspermatogenesis in testes as well as vesiculitis of seminal vesicles. Vesiculitis of seminal vesicles and edema of the testes were also seen in rats treated for 2 years at 18 mg/kg/day (approximately 4 times the human C_{max} achieved with a 40 milligram daily dose).

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Fluvastatin sodium produced delays in skeletal development in rats at doses of 12 mg/kg/day and in rabbits at doses of 10 mg/kg/day. Malaligned thoracic vertebrae were seen in rats at 36 mg/kg, a dose that produced maternal toxicity. These doses resulted in 2 times (rat at 12 mg/kg) or 5 times (rabbit at 10 mg/kg) the 40 mg human exposure based on mg/m² surface area. A study in which female rats were dosed during the third trimester at 12 and 24 mg/kg/day resulted in maternal mortality at or near term and postpartum. In addition, fetal and neonatal lethality were apparent. No effects on the dam or fetus occurred at 2 mg/kg/day. A second study at levels of 2, 6, 12 and 24 mg/kg/day confirmed the findings in the first study with neonatal mortality beginning at 6 mg/kg. A modified Segment III study was performed at dose levels of 12 or 24 mg/kg/day with or without the presence of concurrent supplementation with mevalonic acid, a product of HMG-CoA reductase which is essential for cholesterol biosynthesis. The concurrent administration of mevalonic acid completely prevented the maternal and neonatal mortality but did not prevent low body weights in pups at 24 mg/kg on days 0 and 7 postpartum. Therefore, the maternal and neonatal lethality observed with fluvastatin sodium reflect its exaggerated pharmacologic effect during pregnancy. There are no data with fluvastatin sodium in pregnant women. However, rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took another HMG-CoA reductase inhibitor with dextroamphetamine sulfate during the first trimester of pregnancy. **Lescol® (fluvastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If a woman becomes pregnant while taking Lescol® (fluvastatin sodium), the drug should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers

Based on preclinical data, drug is present in breast milk in a 2:1 ratio (milk:plasma). Because of the potential for serious adverse reactions in nursing infants, nursing women should not take Lescol® (fluvastatin sodium) *(see CONTRAINDICATIONS).*

Pediatric Use

Safety and effectiveness in individuals less than 18 years old have not been established. Treatment in patients less than 18 years of age is not recommended at this time.

Geriatric Use

The effect of age on the pharmacokinetics of fluvastatin sodium was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary either as a function of age or gender. *(See also CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism.)* Elderly patients (≥65 years of age) demonstrated a greater treatment response in respect to LDL-C, Total-C and LDL/HDL ratio than patients <65 years of age.

ADVERSE REACTIONS

In all clinical studies, 1.0% (32/2969) of fluvastatin treated patients were discontinued due to adverse experiences attributed to study drug (mean exposure approximately 16 months ranging in duration from 1 to >36 months). This results in controlled studies in an exposure adjusted rate of 0.8% (32/4051) per patient year in fluvastatin patients compared to an incidence of 1.1% (4/355) in placebo patients. Adverse reactions have usually been of mild to moderate severity.

Adverse experiences occurring in controlled studies with a frequency >2% regardless of causality include the following:

Adverse Event	Lescol® (fluvastatin sodium) (%) (N=2326)	Placebo (%) (N=960)
Integumentary		
Rash	2.3	2.4
Musculoskeletal		
Back Pain	5.7	6.6
Myalgia	5.0	4.5
Arthralgia	4.0	4.1
Arthritis	2.1	2.0
Respiratory		
Upper Respiratory Tract Infection	16.2	16.5
Pharyngitis	3.8	3.8
Rhinitis	4.7	4.9
Sinusitis	2.6	1.9
Coughing	2.4	2.9
Gastrointestinal		
Dyspepsia	7.9	3.2
Diarrhea	4.9	4.2
Abdominal Pain	4.9	3.8
Nausea	3.2	2.0
Constipation	3.1	3.3
Flatulence	2.6	2.5
Misc. Tooth Disorder	2.1	1.7
Central Nervous System		
Dizziness	2.2	2.5
Psychiatric Disorders		
Insomnia	2.7	1.4
Miscellaneous		
Headache	8.9	7.8
Influenza-Like Symptoms	5.1	5.7
Accidental Trauma	5.1	4.8
Fatigue	2.7	2.3
Allergy	2.3	2.2

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with fluvastatin sodium therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

Concomitant Therapy

Fluvastatin sodium has been administered concurrently with cholestyramine and nicotinic acid. No adverse reactions unique to the combination or in addition to those previously reported for this class of drugs alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. *(See WARNINGS: Skeletal Muscle.)*

OVERDOSAGE

The approximate oral LD_{50} is greater than 2 g/kg in mice and greater than 0.7 g/kg in rats.

The maximum single oral dose received by healthy volunteers was 60 mg. No clinically significant adverse experiences were seen at this dose. There has been a single report of 2 children, one 2 years old and the other 3 years of age, either of whom may have possibly ingested fluvastatin sodium. The maximum amount of fluvastatin sodium that could have been ingested was 80 mg (4 × 20 mg capsules). Vomiting was induced by ipecac in both children and no capsules were noted in their emesis. Neither child experienced any adverse symptoms and both recovered from the incident without problems.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. The dialyzability of fluvastatin sodium and of its metabolites in humans is not known at present.

Information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Regional Poison Control Centers are listed in the Physicians' Desk Reference®.*

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving Lescol® (fluvastatin sodium) and should continue on this diet during treatment with Lescol® (fluvastatin sodium). (See NCEP Treatment Guidelines for details on dietary therapy.)

The recommended starting dose for the majority of patients is 20-40 mg once daily at bedtime. The recommended dosing range is 20-80 mg/day. The daily regimen of 80 mg should be administered in divided doses, i.e., 40 mg b.i.d., and should be reserved for those whose LDL-cholesterol response is inadequate at 40 mg/day. Lescol® (fluvastatin sodium) may be taken without regard to meals, since there are no apparent differences in the lipid-lowering effects of fluvastatin sodium administered with the evening meal or 4 hours after the evening meal. Since the maximal reductions in LDL-C of a given dose are seen within 4 weeks, periodic lipid determinations should be performed and dosage adjustment made according to the patient's response to therapy and established treatment guidelines. The therapeutic effect of Lescol® (fluvastatin sodium) is maintained with prolonged administration.

Concomitant Therapy
Lipid-lowering effects on total cholesterol and LDL cholesterol are additive when Lescol® (fluvastatin sodium) is combined with a bile-acid binding resin or niacin. When administering a bile-acid resin (e.g., cholestyramine) and fluvastatin sodium, Lescol® (fluvastatin sodium) should be administered at bedtime, at least 2 hours following the resin to avoid a significant interaction due to drug binding to resin. *(See also ADVERSE REACTIONS: Concomitant Therapy.)*

Dosage in Patients with Renal Insufficiency
Since fluvastatin sodium is cleared hepatically with less than 6% of the administered dose excreted into the urine, dose adjustments for mild to moderate renal impairment are not necessary. Caution should be exercised with severe impairment.

HOW SUPPLIED
Lescol® (fluvastatin sodium) Capsules

20 mg
Brown and light brown imprinted twice with " Δ " and "20" on one half and "LESCOL" and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.

Bottles of 30 capsules (NDC 0078-0176-15)
Bottles of 100 capsules (NDC 0078-0176-05)

40 mg
Brown and gold imprinted twice with " Δ " and "40" on one half and "LESCOL" and the Lescol® (fluvastatin sodium) logo twice on the other half of the capsule.

Bottles of 30 capsules (NDC 0078-0234-15)
Bottles of 100 capsules (NDC 0078-0234-05)

Store and Dispense
Below 86°F (30°C) in a tight container. Protect from light.

*Trademark of Medical Economics Company, Inc.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

666800
30753908 PRINTED IN USA C98-27 (Rev. 6/98)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-261/S019

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

APPROVED

Labeling Review

JAN 4 1999

Application Number: NDA 20-261/S-19

Name of Drug: Lescol (fluvastatin sodium) Capsules

Sponsor: Novartis

Materials Reviewed: September 25, 1997 last approved labeling approved October 1, 1997 (S-012) and August 4, 1998 final printed labeling for supplement-019.

Supplement-019 was the response by Norvartis to the March 2, 1998 fax requesting that all manufacturers of marketed HMG-CoA reductase inhibitors remove the last paragraph in the PRECAUTIONS, Drug Interactions section titled "Other Concomitant Therapy or Other Drugs".

Requested change for supplement -019 was accepted in the August 4, 1998 submission. This change was accepted by the reviewing team. This is Novartis C98-27 (Rev.6/98) 666800; 30753908.

Medical Reviewer _____ 1/4/99

Medical Team Leader D. Orloff 1-4-99

Chemistry Reviewer _____ 11/25/98

Chemistry Team Leader Stephen K. Moore 11/24/98

Pharmacology Team Leader Ronald W. Stewart 11/30/98

Biopharm Team Leader _____ 11/24/98

Project Manager Maryann Lamoreaux

Chief, Project Manager _____ 12/31/98

cc: Original NDA 20-261/S-019
DivFile

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-261/S-019

Novartis Pharm
59 Route 10
East Hanover, NJ 07936

AUG 19 1998

Attention: Jerry Klimek
Associate Director
Drug Regulatory Affairs

Dear Mr. Klimek:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Lescol® (Fluvastatin Sodium)
NDA Number:	20-261
Supplement Number:	S-019
Date of Supplement:	August 4, 1998
Date of Receipt:	August 10, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 9, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

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

Sincerely,

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

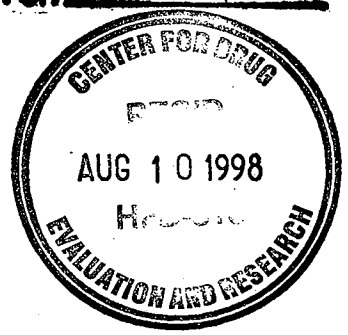
cc:
Original NDA 20-261/S-019
HFD-510/Div. Files
HFD-510/CSO/M. Simoneau

filename:

SUPPLEMENT ACKNOWLEDGEMENT

ORIGINAL APPROVED NDA NO. 20261 REF. NO. 019
NDA SUPPL FOR SLR

NOVARTIS



August 4, 1998

NDA SUPPLEMENT

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

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

Change Being Effected (CBE)
Labeling Supplement
FINAL PRINTED LABELING
8/17/98

Noted 9/1/98
FAX sent 3/2/98.

Dear Dr. Sobel:

Reference is made to a FDA telefax dated March 2, 1998 requesting that all manufacturers of marketed HMG-CoA reductase inhibitors remove the last paragraph in the PRECAUTIONS, Drug Interactions section titled "Other Concomitant Therapy or Other Drugs".

We are providing with this correspondence fifteen (15) copies of Final Printed Labeling for Lescol® (fluvastatin sodium) Capsules where the requested FDA change has been made. We will be implementing use of this newly revised package insert (No. 30753908) on or about September 1st.

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

PC
RWStagewait
9/1/98

REVIEWS COMPLETED
Apltr - Jan 4, 99
CSO ACTION:
☑ LETTER ☐ N.A.I. ☐ MEMO
Nies 1/5/99
CSO INITIALS DATE

Sincerely,

Jerry Klimek
Associate Director
Drug Regulatory Affairs

Attachments: 15 Copies of Lescol® package insert (Rev. 6/98, 666800, No. 30753908)

9/1/98