CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-316

CORRESPONDENCE

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

Table V
NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD[†] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)[††]
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor[†††]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[†] CHD, coronary heart disease
[††] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
[†††] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dL (see NCEP Guidelines above).

MESSAGE CONFIRMATION

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

DATE: June 26, 2002

APPEARS THIS WAY
ON ORIGINAL

Comments:
Attached is a copy of correspondence from the Division regarding NDA 21-316. The original letter will be sent by mail.

Don't hesitate to call with any questions.

TO: **FROM:**

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Draft

Labeling

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LOVASTATIN TABLETS USP

Rev. E 11/2001

0324

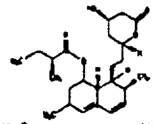
GENERIC Lovastatin Label

APPROVED

DEC 17 2001

Lovastatin is a cholesterol lowering agent isolated from a strain of *Aspergillus terreus*. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

Lovastatin is [1 S-[1α(R*), 3α,7β,8β (2 S*,4 S*), 8aβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. Its structural formula is:



$C_{24}H_{36}O_5$ M.W. 404.55

Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile.

Lovastatin Tablets are supplied as 10 mg, 20 mg or 40 mg tablets for oral administration. In addition, each tablet contains the following inactive ingredients: lactose monohydrate, pregelatinized starch, magnesium stearate, and microcrystalline cellulose. Butylated hydroxyanisole (BHA) is added as a preservative. Lovastatin Tablets, 10 mg also contain FD&C Yellow #6. Lovastatin Tablets, 20 mg also contain FD&C Blue #1. Lovastatin Tablets, 40 mg also contain D&C Yellow #10, FD&C Blue #1, and FD&C Yellow #6.

CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological and clinical studies have established that high LDL-C and low high-density lipoprotein cholesterol (HDL-C) are both associated with coronary heart disease. However, the risk of developing coronary heart disease is continuous and graded over the range of cholesterol levels and many coronary events do occur in patients with total cholesterol (total-C) and LDL-C in the lower end of this range.

Lovastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very low-density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of lovastatin may involve both reduction of VLDL-C concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with lovastatin. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that lovastatin does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, lovastatin can produce increases of variable magnitude in HDL-C, and modestly reduces VLDL-C and plasma triglycerides (TG) (see Tables I-III under *Clinical Studies*). The effects of lovastatin on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

Lovastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

Pharmacokinetics

Lovastatin is a lactone which is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of lovastatin.

Following an oral dose of ^{14}C-labeled lovastatin in man, 10% of the dose was excreted in urine and 83% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (lovastatin plus ^{14}C-metabolites) peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours postdose. Absorption of lovastatin, estimated relative to an intravenous reference dose, in each of four animal species tested, averaged about 30% of an oral dose. In animal studies, after oral dosing, lovastatin had high selectivity for the liver, where it achieved substantially higher concentrations than in non-target tissues. Lovastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of lovastatin, the availability of drug to the general circulation is low and variable. In a single dose study in four hypercholesterolemic patients, it was estimated that less than 5% of an oral dose of lovastatin reaches the general circulation as active inhibitors. Following administration of lovastatin tablets the coefficient of variation, based on between-subject variability, was approximately 40% for the area under the curve (AUC) of total inhibitory activity in the general circulation.

Both lovastatin and its β-hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Animal studies demonstrated that lovastatin crosses the blood-brain and placental barriers.

The major active metabolites present in human plasma are the β-hydroxyacid of lovastatin, its 6'-hydroxy derivative, and two additional metabolites. Peak plasma concentrations of both active and total inhibitors were attained within 2 to 4 hours of dose administration. While the recommended therapeutic dose range is 10 to 80 mg/day, linearity of inhibitory activity in the general circulation was established by a single dose study employing lovastatin tablet dosages from 60 to as high as 120 mg. With a once-a-day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady state between the second and third days of therapy and were about 1.5 times those following a single dose. When lovastatin was given under fasting conditions, plasma concentrations of total inhibitors were on average about two-thirds those found when lovastatin was administered immediately after a standard test meal.

In a study of patients with severe renal insufficiency (creatinine clearance 10-30 mL/min), the plasma concentrations of total inhibitors after a single dose of lovastatin were approximately two-fold higher than those in healthy volunteers.

In a study including 16 elderly patients between 70-78 years of age who received lovastatin 80 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age (see **PRECAUTIONS**, *Geriatric Use*).

Lovastatin is a substrate for cytochrome P450 isoform 3A4 (CYP3A4) (see **PRECAUTIONS**, *Drug Interactions*). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study**, 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 80 mg lovastatin on the third day. This regimen of grapefruit juice resulted in a mean increase in the serum concentration of lovastatin and its β-hydroxyacid metabolite (as measured by the area under the concentration-time curve) of 15-fold and 5-fold, respectively [as measured using chemical assay - high performance liquid chromatography]. In a second study, 15 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 40 mg lovastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using an enzyme inhibition assay both before (for active inhibitors) and after

of lovastatin and its β-hydroxyacid metabolite [measured using a ch… liquid chromatography/tandem mass spectrometry - different from t… first** study] of 1.34-fold and 1.57-fold, respectively. The effect … grapefruit juice between those used in these two studies on lovasta… kinetics has not been studied.

**Kantola, T. et al., Clin Pharmacol Ther 1998;63(4):397-402.

Clinical Studies

Lovastatin has been shown to be highly effective in reducing total-C… heterozygous familial and non-familial forms of primary hypercholes… in mixed hyperlipidemia. A marked response was seen within 2 w… maximum therapeutic response occurred within 4-6 weeks. The … maintained during continuation of therapy. Single daily doses given … were more effective than the same dose given in the morning, per… cholesterol is synthesized mainly at night.

In multicenter, double-blind studies in patients with familial or non-f… cholesterolemia, lovastatin, administered in doses ranging from 10… 40 mg b.i.d., was compared to placebo. Lovastatin consistently an… decreased plasma total-C, LDL-C, total-C/HDL-C ratio and LDL-C/HD… addition, lovastatin produced increases of variable magnitude in HDL-C, … decreased VLDL-C and plasma TG. (see Tables I through III for d… results)

The results of a study in patients with primary hypercholesterolemia… in Table I.

TABLE I

Lovastatin vs. Placebo

(Mean Percent Change from Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C
Placebo	33	-2	-1	-1	0	[illegible]
Lovastatin						
10 mg q.p.m.	33	-16	-21	+5	-24	-1
20 mg q.p.m.	33	-19	-27	+6	-30	-2
10 mg b.i.d.	32	-19	-28	+8	-33	-2
40 mg q.p.m.	33	-22	-31	+5	-33	-2
20 mg b.i.d.	36	-24	-32	+2	-32	-2

Lovastatin was compared to cholestyramine in a randomized open … The study was performed with patients with hypercholesterolemia … high risk of myocardial infarction. Summary results are presented in…

TABLE II

Lovastatin vs. Cholestyramine

(Percent Change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VL… (me…)
Lovastatin							
20 mg b.i.d.	85	-27	-32	+9	-36	-31	[illegible]
40 mg b.i.d.	88	-34	-42	+8	-44	-37	[illegible]
Cholestyramine							
12 g b.i.d.	88	-17	-23	+8	-27	-21	[illegible]

Lovastatin was studied in controlled trials in hypercholesterolemic … well-controlled non-insulin dependent diabetes mellitus with normal r… The effect of lovastatin on lipids and lipoproteins and the safety profil… were similar to that demonstrated in studies in nondiabetics. Lova… clinically important effect on glycemic control or on the dose requir… hypoglycemic agents.

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

Lovastatin was compared to placebo in 8,245 patients with hyperch… (total-C 240-300 mg/dL [6.2 mmol/L-7.8 mmol/L], LDL-C>160 mg/dL [… in the randomized, double-blind, parallel, 48-week EXCEL study. All … lipid measurements (Table III) in lovastatin treated patients were dos… significantly different from placebo (p≤0.001). These results we… throughout the study.

TABLE III

Lovastatin vs. Placebo

(Percent Change from Baseline -

Average Values Between Weeks 12 and 48)

DOSAGE	N**	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTA… HDL… (me…)
Placebo	1663	+0.7	+0.4	+2.0	-0.2	+0…
Lovastatin						
20 mg q.p.m.	1642	-17	-24	+6.6	-27	-21
40 mg q.p.m.	1645	-22	-30	+7.2	-34	-26
20 mg b.i.d.	1646	-24	-34	+8.6	-38	-2…
40 mg b.i.d.	1649	-29	-40	+9.5	-44	-3…

**Patients enrolled

Atherosclerosis

In the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), … therapy with lovastatin on coronary atherosclerosis was assessed … angiography in hyperlipidemic patients. In the randomized, doubl… trolled clinical trial, patients were treated with conventional measures … and 325 mg of aspirin every other day) and either lovastatin 20-80 … placebo. Angiograms were evaluated at baseline and at two years by c… quantitative coronary angiography (QCA). Lovastatin significantly slo… gression of lesions as measured by the mean change per-patient i… lumen diameter (the primary endpoint) and percent diameter st… decreased the proportions of patients categorized with disease progr… vs. 50%) and with new lesions (16% vs. 32%).

In a similarly designed trial, the Monitored Atherosclerosis Regre… (MARS), patients were treated with diet and either lovastatin 80 mg dail… No statistically significant difference between lovastatin and placebo … the primary endpoint (mean change per patient in percent diameter st… lesions), or for most secondary QCA endpoints. Visual assessment by a… who formed a consensus opinion of overall angiographic change (Gl… Score) was also a secondary endpoint. By this endpoint, significant slowi… was seen, with regression in 23% of patients treated with lovastatin c… 11% of placebo patients.

In the Familial Atherosclerosis Treatment Study (FATS), either lovasta… in combination with a bile acid sequestrant for 2.5 years in hyperlipiden… significantly reduced the frequency of progression and increased the f… regression of coronary atherosclerotic lesions by QCA compared to … some cases, low-dose resin.

The effect of lovastatin on the progression of atherosclerosis in the coro… has been corroborated by similar findings in another vasculatu… Asymptomatic Carotid Artery Progression Study (ACAPS), the effec… with lovastatin on carotid atherosclerosis was assessed by B-mode ult… in hyperlipidemic patients with early carotid lesions and without know… heart disease at baseline. In this double-blind, controlled clinical trial, … were randomized in a 2 x 2 factorial design to placebo, lovastatin 10-… and/or warfarin. Ultrasonograms of the carotid walls were used to d… change per patient from baseline to three years in mean maximum in… thickness (IMT) of 12 measured segments. There was a significant r…

of lovastatin and its β-hydroxyacid metabolite (measured using a chemical assay-liquid chromatography/tandem mass spectrometry - different from that used in the first** study) of 1.94-fold and 1.57-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied.

**Kantola, T. et al., Clin Pharmacol Ther 1998;63(4):397-402.

Clinical Studies

Lovastatin has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of primary hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during continuation of therapy. Single daily doses given in the evening were more effective than the same dose given in the morning, perhaps because cholesterol is synthesized mainly at night.

In multicenter, double-blind studies in patients with familial or non-familial hypercholesterolemia, lovastatin, administered in doses ranging from 10 mg q.p.m. to 40 mg b.i.d., was compared to placebo. Lovastatin consistently and significantly decreased plasma total-C, LDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio. In addition, lovastatin produced increases of variable magnitude in HDL-C, and modestly decreased VLDL-C and plasma TG (see Tables I through III for dose response results).

The results of a study in patients with primary hypercholesterolemia are presented in Table I.

TABLE I
Lovastatin vs. Placebo
(Mean Percent Change from Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	TG.
Placebo	33	-2	-1	-1	0	+1	+9
Lovastatin							
10 mg q.p.m.	33	-16	-21	+5	-24	-19	-10
20 mg q.p.m.	33	-19	-27	+6	-30	-23	-9
10 mg b.i.d.	32	-19	-28	+8	-33	-25	-7
40 mg q.p.m.	33	-22	-31	+5	-33	-25	-8
20 mg b.i.d.	36	-24	-32	+2	-32	-24	-6

Lovastatin was compared to cholestyramine in a randomized open parallel study. The study was performed with patients with hypercholesterolemia who were at high risk of myocardial infarction. Summary results are presented in Table II.

TABLE II
Lovastatin vs. Cholestyramine
(Percent Change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TG. (mean)
Lovastatin								
20 mg b.i.d.	85	-27	-32	+9	-36	-31	-34	-21
40 mg b.i.d.	88	-34	-42	+8	-44	-37	-31	-27
Cholestyramine								
12 g b.i.d.	88	-17	-23	+8	-27	-21	+2	+11

Lovastatin was studied in controlled trials in hypercholesterolemic patients with well-controlled non-insulin dependent diabetes mellitus with normal renal function. The effect of lovastatin on lipids and lipoproteins and the safety profile of lovastatin were similar to that demonstrated in studies in nondiabetics. Lovastatin had no clinically important effect on glycemic control or on the dose requirement of oral hypoglycemic agents.

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

Lovastatin was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2 mmol/L-7.6 mmol/L], LDL-C >160 mg/dL [4.1 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. All changes in the lipid measurements (Table III) in lovastatin treated patients were dose-related and significantly different from placebo (p≤0.001). These results were sustained throughout the study.

TABLE III
Lovastatin vs. Placebo
(Percent Change from Baseline - Average Values Between Weeks 12 and 48)

DOSAGE	N**	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TG. (median)
Placebo	1663	-0.7	-0.4	+2.0	-0.2	+0.6	+4
Lovastatin							
20 mg q.p.m.	1642	-17	-24	+6.6	-27	-21	-10
40 mg q.p.m.	1645	-22	-30	+7.2	-34	-26	-14
20 mg b.i.d.	1646	-24	-34	+8.6	-38	-29	-16
40 mg b.i.d.	1649	-29	-40	+9.5	-44	-34	-19

**Patients enrolled

Atherosclerosis

In the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), the effect of therapy with lovastatin on coronary atherosclerosis was assessed by coronary angiography in hyperlipidemic patients. In the randomized, double-blind, controlled clinical trial, patients were treated with conventional measures (usually diet and 325 mg of aspirin every other day) and either lovastatin 20-80 mg daily or placebo. Angiograms were evaluated at baseline and at two years by computerized quantitative coronary angiography (QCA). Lovastatin significantly slowed the progression of lesions as measured by the mean change per-patient in minimum lumen diameter (the primary endpoint) and percent diameter stenosis, and decreased the proportions of patients categorized with disease progression (33% vs. 50%) and with new lesions (16% vs. 32%).

In a similarly designed trial, the Monitored Atherosclerosis Regression Study (MARS), patients were treated with diet and either lovastatin 80 mg daily or placebo. No statistically significant difference between lovastatin and placebo was seen for the primary endpoint (mean change per patient in percent diameter stenosis of all lesions), or for most secondary QCA endpoints. Visual assessment by angiographers who formed a consensus opinion of overall angiographic change (Global Change Score) was also a secondary endpoint. By this endpoint, significant slowing of disease was seen, with regression in 23% of patients treated with lovastatin compared to 11% of placebo patients.

In the Familial Atherosclerosis Treatment Study (FATS), either lovastatin or niacin in combination with a bile acid sequestrant for 2.5 years in hyperlipidemic subjects significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions by QCA compared to diet and, in some cases, low-dose resin.

The effect of lovastatin on the progression of atherosclerosis in the coronary arteries has been corroborated by similar findings in another vasculature. In the Asymptomatic Carotid Artery Progression Study (ACAPS), the effect of therapy with lovastatin on carotid atherosclerosis was assessed by B-mode ultrasonography in hyperlipidemic patients with early carotid lesions and without known coronary heart disease at baseline. In this double-blind, controlled clinical trial, 919 patients were randomized in a 2 x 2 factorial design to placebo, lovastatin 10-40 mg daily and/or warfarin. Ultrasonograms of the carotid walls were used to determine the change per patient from baseline to three years in mean maximum intimal-medial thickness (IMT) of 12 measured segments. There was a significant regression of [illegible] placebo alone (p=0.001). The predictive value of changes in IMT for [illegible] has not yet been established. In the lovastatin group there was a significant reduction in the number of patients with major cardiovascular events relative to the placebo group (5 vs. 14) and a significant reduction in all-cause mortality (1 vs. 8).

Eye

There was a high prevalence of baseline lenticular opacities in the patient population included in the early clinical trials with lovastatin. During these trials the appearance of new opacities was noted in both the lovastatin and placebo groups. There was no clinically significant change in visual acuity in the patients who had new opacities reported nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity.

A three-year, double-blind, placebo-controlled study in hypercholesterolemic patients to assess the effect of lovastatin on the human lens demonstrated that there were no clinically or statistically significant differences between the lovastatin and placebo groups in the incidence, type or progression of lenticular opacities. There are no controlled clinical data assessing the lens available for treatment beyond three years.

INDICATIONS AND USAGE

Therapy with lovastatin should be a component of multiple risk factor intervention in those individuals with dyslipidemia at risk for atherosclerotic vascular disease. Lovastatin should be used in addition to a diet restricted in saturated fat and cholesterol as part of a treatment strategy to lower total-C and LDL-C to target levels when the response to diet and other nonpharmacological measures alone has been inadequate to reduce risk.

Coronary Heart Disease

Lovastatin is indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total-C and LDL-C to target levels.

Hypercholesterolemia

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lovastatin is indicated as an adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb***), when the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.

General Recommendations

Prior to initiating therapy with lovastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

$$LDL\text{-}C = total\text{-}C - [0.2 \times (TG) + HDL\text{-}C]$$

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 hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, lovastatin is not indicated.

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

NCEP Treatment Guidelines:
LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2+ Risk factors (10-year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130; 10-year risk <10%: ≥160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

† CHD, coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

After the LDL-C goal has been achieved, if the TG is still ≥200 mg/dL, non-HDL-C (total-C minus HDL-C) becomes a secondary target of therapy. Non-HDL-C goals are set 30 mg/dL higher than LDL-C goals for each risk category.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dL (see NCEP Guidelines above).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that 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.

Although lovastatin may be useful to reduce elevated LDL-C levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it 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.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as lovastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, lovastatin is contraindicated during pregnancy and in nursing mothers. Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug, lovastatin should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, Pregnancy).

WARNINGS

Skeletal Muscle

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (> 10x the upper limit of normal [ULN]). Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported [illegible] weeks, and 4 among 1649 patients randomized to 80 mg daily. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and creatine kinase (CK) increases promptly resolved. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the EXCEL study design.

Myopathy caused by drug interactions

The incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid).

In addition, the risk of myopathy may be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Lovastatin is metabolized by the cytochrome P450 isoform 3A4 (CYP3A4). Potent inhibitors of this metabolic pathway can raise the plasma level of HMG-CoA reductase inhibitory activity and may increase the risk of myopathy. These include cyclosporine, the azole antifungals, itraconazole and ketoconazole; the macrolide antibiotics, erythromycin and clarithromycin; HIV protease inhibitors; the antidepressant nefazodone; and large quantities of grapefruit juice (>1 quart daily) (see below, CLINICAL PHARMACOLOGY, *Pharmacokinetics*; PRECAUTIONS, *Drug Interactions*; and DOSAGE AND ADMINISTRATION).

Although the data are insufficient for lovastatin, the risk of myopathy appears to be increased when verapamil is used concomitantly with a closely related HMG-CoA reductase inhibitor (see PRECAUTIONS, Drug Interactions).

Reducing the risk of myopathy

1. General measures. Patients starting therapy with lovastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness. A creatine kinase (CK) level above 10x ULN in a patient with unexplained muscle symptoms indicates myopathy. Lovastatin therapy should be discontinued if myopathy is diagnosed or suspected. In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved.

Of the patients with rhabdomyolysis, many had complicated medical histories. Some had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with lovastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. Measures to reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS, *Drug Interactions*). Physicians contemplating combined therapy with lovastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of lovastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of lovastatin have been used without myopathy in small, short-term clinical trials with careful monitoring. Addition of these drugs to lovastatin typically provides little additional reduction in LDL cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with lovastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of lovastatin should generally not exceed 20 mg/day (see DOSAGE AND ADMINISTRATION and DOSAGE AND ADMINISTRATION, *Concomitant Lipid-Lowering Therapy*), as the risk of myopathy increases substantially at higher doses. Concomitant use of lovastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) is not recommended. If no alternative to a short course of treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is available, a brief suspension of lovastatin therapy during such treatment can be considered as there are no known adverse consequences to brief interruptions of long-term cholesterol-lowering therapy.

Liver Dysfunction

Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin, and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the incidence of persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with lovastatin, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

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 of dose, and periodically thereafter (e.g., semiannually). 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 therapy with lovastatin is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with lovastatin (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with lovastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

PRECAUTIONS

General

Lovastatin may elevate 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 lovastatin.

Homozygous Familial Hypercholesterolemia

Lovastatin is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. Lovastatin appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness (see WARNINGS, *Skeletal Muscle*).

Drug Interactions

Gemfibrozil and other fibrates, lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid): These drugs increase the risk of myopathy when given concomitantly with lovastatin, probably because they can produce myopathy when given alone (see WARNINGS, *Skeletal Muscle*). There is no evidence to suggest that these agents affect the pharmacokinetics of lovastatin.

CYP3A4. However, lovastatin itself is a substrate for CYP3A4. Potent inhibitors of CYP3A4 may increase the risk of myopathy by increasing the plasma concentration of HMG-CoA reductase inhibitory activity during lovastatin therapy. These inhibitors include cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone and large quantities of grapefruit juice (> 1 quart daily) (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Skeletal Muscle*).

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. Large quantities of grapefruit juice (>1 quart daily) significantly increased the serum concentrations of lovastatin and its β-hydroxyacid metabolic during lovastatin therapy and should be avoided (see CLINICAL PHARMACOLOGY, *Pharmacokinetics* and WARNINGS, *Skeletal Muscle*).

Although the data are insufficient for lovastatin, the risk of myopathy appears to be increased when verapamil is used concomitantly with a closely related HMG-CoA reductase inhibitor (see WARNINGS, *Skeletal Muscle*).

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two-second increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Oral Hypoglycemic Agents: In pharmacokinetic studies of lovastatin in hypercholesterolemic non-insulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effect, if any, on the pituitary-gonadal axis in pre-menopausal women is unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity

Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinal ganglion cell axons) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated ~14 weeks at 180 mg/kg/day, a dose which resulted in mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

5 vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose which produced plasma drug levels (C_{max}) which were about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Cataracts were seen in dogs treated for 11 and 28 weeks at 180 mg/kg/day and 1 year at 60 mg/kg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinoma and adenoma in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of lovastatin.)

There was an increase in incidence of papilloma in the non-glandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males at drug exposures between 2-7 times that of human exposure at 80 mg/day (doses in rats were 5, 30 and 180 mg/kg/day).

An increased incidence of thyroid neoplasms in rats appears to be a response that has been seen with other HMG-CoA reductase inhibitors.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high dose females and mid- and high dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high dose mice than in controls.

No evidence of mutagenicity was observed in a microbial assay test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy; Teratogenic effects

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in other species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to lovastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with lovastatin during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. Lovastatin 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.

Nursing Mothers

It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking lovastatin should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with lovastatin is not recommended at this time.

Geriatric Use

A pharmacokinetic study with lovastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age; however, clinical study experience in the elderly indicates that dosage adjustment based on this age-related pharmacokinetic difference is not needed. In clinical studies conducted with lovastatin 21% of patients were ≥65 years of age. Lipid-lowering efficacy with lovastatin was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg/day dosage range (see CLINICAL PHARMACOLOGY).

† Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy. *Reproductive Toxicology* 10(6): 439-446, 1996.

ADVERSE REACTIONS

Lovastatin is generally well tolerated; adverse reactions usually have been mild and transient.

Phase III Clinical Studies

In Phase III controlled clinical studies involving 613 patients treated with lovastatin, the adverse experience profile was similar to that shown below for the 8,245-patient EXCEL study (see *Expanded Clinical Evaluation of Lovastatin (EXCEL) Study*).

Persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 11% of patients had elevations of CK levels of at least twice the normal value on one or more occasions. The corresponding values for the control agent cholestyramine was 9 percent. This was attributable to the noncardiac fraction of CK. Large increases in CK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

Lovastatin was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2-7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably or definitely drug-related in ≥1% in any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

	Placebo (N = 1663) %	Lovastatin 20 mg q.p.m (N = 1642) %	Lovastatin 40 mg q.p.m. (N = 1645) %	Lovastatin 20 mg b.i.d. (N = 1646) %	Lovastatin 40 mg b.i.d. (N = 1649) %
Body As a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.8	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.8
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.8	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.9	1.1	0.8	0.9	1.2

Other clinical adverse experiences reported as possibly, probably or definitely drug-related in 0.5 to 1.0 percent of patients in any drug-treated group are listed below. In all these cases the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthritis; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences which were rated by the investigator as possibly, probably or

Concomitant Therapy

In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggests that the addition of gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL-C than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with cyclosporine, gemfibrozil or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

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

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

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 erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, 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.

OVERDOSAGE

After oral administration of lovastatin to mice the median lethal dose observed was >15 g/m².

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients has any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5-8 g.

Until further experience is obtained, no specific treatment of overdosage with lovastatin can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving lovastatin and should continue on this diet during treatment with lovastatin (see NCEP Treatment Guidelines for details on dietary therapy). Lovastatin should be given with meals.

The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 10-80 mg/day in single or two divided doses; the maximum recommended dose is 80 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Guidelines and CLINICAL PHARMACOLOGY). Patients requiring reductions in LDL-C of 30% or more to achieve their goal (see INDICATIONS AND USAGE) should be started on 20 mg/day of lovastatin. A starting dose of 10 mg may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.

In patients taking cyclosporine drugs concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of lovastatin and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of lovastatin if cholesterol levels fall significantly below the targeted range.

Concomitant Lipid-Lowering Therapy

Lovastatin is effective alone or when used concomitantly with bile-acid sequestrants. Use of lovastatin with fibrates or niacin should generally be avoided. However, if lovastatin is used in combination with fibrates or niacin, the dose of lovastatin should generally not exceed 20 mg/day (see WARNINGS, *Skeletal Muscle* and PRECAUTIONS, *Drug Interactions*).

Dosage in Patients with Renal Insufficiency

In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and if deemed necessary, implemented cautiously (see CLINICAL PHARMACOLOGY and WARNINGS, *Skeletal Muscle*).

HOW SUPPLIED

Lovastatin Tablets USP, 10 mg are available as light peach, round, flat beveled tablets debossed with "926" on the upper surface and "93" on the lower surface. Packaged in bottles of 60, 100 and 1000.

Lovastatin Tablets USP, 20 mg are available as light blue, round, flat beveled tablets, debossed with "576" on the upper surface and "93" on the lower surface. Packaged in bottles of 60, 100, 1000 and 12500.

Lovastatin Tablets USP, 40 mg are available as light green, round, flat beveled tablets, debossed with "928" on the upper surface and "93" on the lower surface. Packaged in bottles of 60, 100, 1000, and 12500.

Store between 5° and 30°C (41° and 86°F). Lovastatin Tablets must be protected from light.

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Rx only

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Printed in USA
Rev. E 11/2001

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DIVISION OF METABOLIC AND
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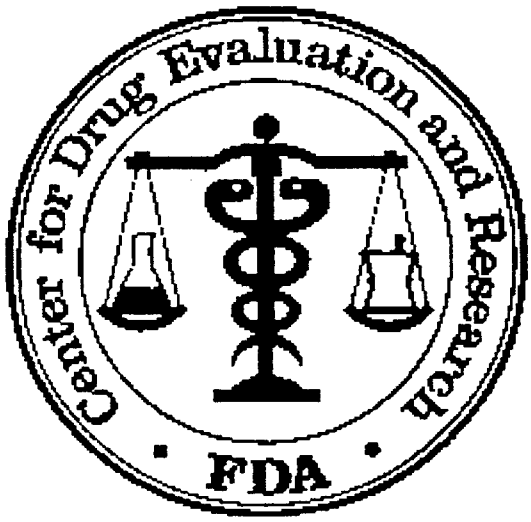
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: December 21, 2001



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Comments:

This is to confirm a scheduled telephone conference
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Date:	January 07, 2002
Time:	11:00 AM

Please supply a conference dial-in number so the Division
can phone you at the appointed time.
Please don't hesitate to call with any questions.

TO:
Name: Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
Fax No.: (201) 883-1893
Phone No.: (610) 428-2417
Location: Aura Laboratories, Inc.

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

Pages (including this cover sheet): forty (40) in three transmissions

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TO: **FROM:**

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NDA 21-316

Altocor (lovastatin) Extended-Release Tablets
Attention: Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
Aura Laboratories, Inc.

We refer to your original NDA submission submitted March 30, 2001.

In regard to the above referenced NDA the Division communicates the following comments from the Biopharmaceutics review team:

> We request that you conduct a drug interaction study comparing the pharmacokinetics of both lovastatin and lovastatin acid with and without concomitant antacid as a postmarketing study commitment. We request that this commitment adhere to the following timeline:
>
> > Final Report Submission: Within 12 months of the date of the action letter.
> >
> > (The Division recommends that a draft protocol of this requested study be submitted to the application in time for the reviewer to provide comments.)
>
> We also request that your commitment to perform this study, as requested, be submitted to the application as an amendment as soon as possible.

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

{See appended electronic signature page}

CLEARED FOR FAXING_____

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

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/s/

William Koch
1/18/02 10:33:25 AM
CSO

Hae-Young Ahn
1/18/02 10:48:07 AM
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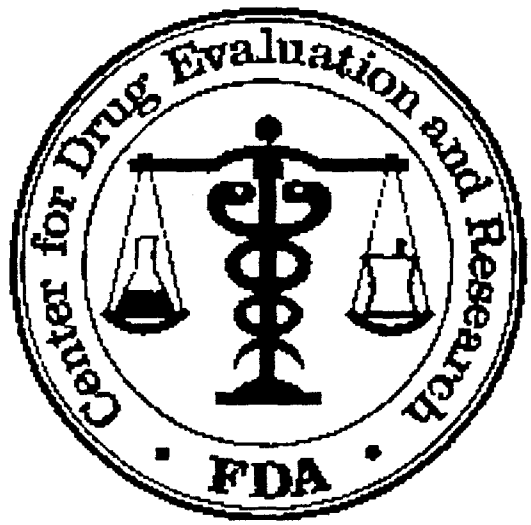
FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: January 18, 2002



APPEARS THIS WAY
ON ORIGINAL

Comments:

Attached are comments from the Division regarding NDA 21-316. A response, submitted to this application, is required.

Please don't hesitate to call with any questions.

TO:
Name: Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
Fax No.: (201) 883-1893
Phone No.: (610) 428-2417
Location: Aura Laboratories, Inc.

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

Pages (including this cover sheet): three (3)

MESSAGE CONFIRMATION

01/18/02 12:33

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Aura
LABORATORIES, INC.

March 30, 2001

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

Subject: ——— (Lovastatin, USP) Extended-Release Tablets NDA No. 21-316

Dear Sir/Madam:

Pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, Aura Laboratories, Inc., a division of Andrx Pharmaceuticals, Inc. located in Fort Lauderdale, Florida hereby submits, in duplicate, for your review and approval a new drug application NDA No. 21-316 to market ——— (Lovastatin, USP) Extended-Release Tablets.

This submission has been provided in paper format. An electronic version of this submission will be sent separately. However, we are submitting an electronic version of Sections 11 and 12 of the NDA, Case Report Form Tabulations and Case Report Forms.

The required User Fee for this product was previously sent to FDA on March 20, 2001.

———Lovastatin, USP) Extended-Release Tablets is a prescription product to be used in those individuals with dyslipidemia who are at risk for atherosclerotic vascular disease.

There is no controlled-release lovastatin product currently approved for sale in the United States.

Aura Laboratories, using both its own data and relying on sources permitted under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, proposes both to retain and to augment in several ways the labeling for the approved immediate-release product

401 Hackensack Avenue • 9th Floor • Hackensack, New Jersey 07601

AN
ANDRX COMPANY

Mevacor® (lovastatin tablets) which is a registered trademark of Merck & Company, Inc. as follows:

(1) Retain appropriate parts of the Mevacor® label that pertain to the lovastatin molecule and "class labeling" relative to safety;

(2) Change parts of the label to reflect ——— specific data (including clinical safety and efficacy data, and clinical pharmacology data);

(3) Change certain other parts of the label based on 505(b)(2) and/or ——— data.

Current indications for ——— that are supported by the new drug application include those that are listed in the Mevacor® full prescribing information, including dyslipidemic indications and ——— These indications are based on the FDA's prior approval of the immediate-release lovastatin product, Mevacor® Tablets (NDA 19-643), marketed by Merck & Company, Inc.

FDA acknowledged the benefits of Section 505(b)(2) applications in its October 1999 draft "Guidance for Industry - Applications Covered by Section 505(b)(2)." The agency stated the 505(b)(2) approach is "intended to encourage innovation [in drug development] without creating duplicate work" and "it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug."

——— Development

Aura Laboratories has pursued its ——— development program because several lines of evidence supported the concept that controlled-release technology would improve the efficacy, and possibly the safety, of lovastatin for pharmaceutical use. These included the following:

- Experimental animal data involving controlled-release statin drugs;
- Favorable Phase 1 and 2 pharmacokinetic and clinical results, supporting continuation into Phase 3 studies; and
- Published Mevacor® data in the EXCEL Trial and in the FDA's original medical officer review of Mevacor®, showing that the same total milligram dose of lovastatin is significantly more effective when administered twice-daily, rather than once-daily.

The ——— development program, including the design of Phase 3 trials, was discussed with the Food and Drug Administration's Metabolic and Endocrine Division at an End-of Phase 2 Meeting, and during Phase 3. Aura's written correspondence with the FDA is included in this application.

Rather than replicating results (including those that pertain to lipids, lipoproteins, apolipoproteins, and to secondary prevention) Aura has relied upon specific, published literature and on prior FDA review of these findings in supplemental NDAs. This includes literature reports corresponding to the major trials cited in the Mevacor® product label. The data also support other, positive changes for the ——— product label. For example, patients treated with ——— required less frequent transaminase monitoring compared with patients given Mevacor®. In addition, the generally recommended starting dose will be higher than that recommended in the Mevacor® product label, reducing the need to titrate the dose to achieve satisfactory lipid reduction, when this is clinically indicated.

NDA No. 21-316 for ——— is submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(b)(2)). A 505(b)(2) application may contain full reports of the safety and effectiveness of a drug product, but at least some of the information may derive from investigations "not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." 21 U.S.C. Section 355(b)(2); see generally 21 C.F.R. Section 314.54.

A Section 505(b)(2) application may rely on published literature and/or prior FDA findings that a different, but related, drug product is safe and effective. In NDA No. 21-316 for ——— , in addition to its own data, Aura relies on both published data and Mevacor® product label (e.g., HDL and TG data from the EXCEL trial) and on the FDA's findings regarding Mevacor®'s safety and effectiveness (including medical officer and other reviews). There is some overlap between some of the referenced data sources: for example, clinical trials such as EXCEL and AFCAPS/TexCAPS were submitted to, and reviewed by, FDA; summary data appear in the product label; and the data also were published in peer-reviewed journals.

Aura independently developed new pre-clinical, clinical, and manufacturing data concerning lovastatin in controlled-release formulation. Specifically, Aura conducted a pre-clinical toxicology trial, and conducted a Phase 1 through 3 clinical program. This program involved two adequate and well-controlled Phase 2 trials, two adequate and well-controlled Phase 3 trials, plus a double-blind extension at higher doses. A total of more than 500 patients were randomized in the two Phase 3 trials.

Patent and Exclusivity Issues

[redacted] Exclusivity

Drugs approved pursuant to Section 505(b)(2) may qualify for periods of market exclusivity. Aura Laboratories submits that, upon approval, [redacted] should qualify for 3 years of exclusivity covering (1) the controlled-release dosage form of lovastatin, and (2) the use of controlled-release lovastatin for "original" indications, including raising HDL and lowering triglycerides. As required by statute and FDA's regulations, Aura has sponsored new clinical investigations that are essential to support these conditions of use of lovastatin. Aura has included a request for 3 years of market exclusivity in NDA No. 21-316.

Patents and Exclusivity Covering Mevacor®

The approval of Section 505(b)(2) applications may be delayed by patents or exclusivity covering referenced products, and NDAs submitted under Section 505(b)(2) must include certifications or statements concerning any such patents or exclusivity. The Orange Book states that Mevacor® is covered by U.S. Patent No. 4,231,938 ("the '938 Patent"), which is scheduled to expire on June 15, 2001. Mevacor® also has been granted 3-year market exclusivity, through March 11, 2002, covering that product's primary prevention indication for patients with below-average HDL.

NDA No. 21-316 includes a "Paragraph III" certification concerning the '938 Patent', stating that Aura does not seek to market [redacted] before the expiration of that patent.

Aura Laboratories, Inc. certifies that in accordance with 21 CFR 314.50(1)(3), a field copy of its New Drug Application, 505(b)(2) for —— Extended-Release Tablets 10, 20, 40, and 60 mgs was concurrently sent to FDA's Florida field office. The field copy is a true copy of the Chemistry, Manufacturing, and Controls technical sections contained in the Archival and Review copies of the application.

We thank you for your cooperation. I can be reached at (610) 428-2417, fax number (201) 883-1893.

Sincerely,

Nicholas J. Farina

Nicholas J. Farina, Ph.D.
Vice President of Regulatory Affairs

Cc: Dr. David Orloff (cover letter only)
Ms. Margaret Simoneau (cover letter only)
Ms. Emma Singleton, Director, Florida District Office, Food and Drug Administration, 555 Winderley Place, Suite 200, Maitland, FL 32751 (cover letter and CMC section)

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2. Revise the phase 4 commitment regarding regulatory criteria for water content and residual solvent in drug product revised to specify that the completed study will be provided to the application as a "Changes Being Effected in 30 Days" supplement and that the cover letter will state "**Postmarketing Commitment - Study Final Report**".

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

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

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Enid Galliers
5/24/02 01:48:26 PM

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Document Information Page

This page is for FDA internal use only. Do NOT send this page with the letter!

Application #(s):	NDA 21-316
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Discipline Review letter for a pending NDA
Shortcut ID Code:	NDA-E2
COMIS Decision:	DR (DISCIPLINE REVIEW)
COMIS Data Entry:	
Drafted by:	WCK/05.22.02
Revised by:	WMAdams05.22.02/SChung05.22.02/EGalliers05.24.02
Initialed by:	STMoore05.23.02/HYAhn05.24.02
Finalized:	WKoch05.24.02
Filename:	C:\WINDOWS\Desktop\NDA21316\LTRdrbph052502.doc
DFS Key Words:	
Notes:	N000
Linking Instructions:	Link this letter to the incoming document containing the information requiring further clarification.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

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

DATE: May 24, 2002

APPEARS THIS WAY
ON ORIGINAL

Comments:

Attached is a copy of correspondence
from the Division regarding NDA 21-316.
The original letter will be sent by mail.

Don't hesitate to call with any questions.

TO:
Name: Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
Fax No.: (201) 883-1893
Phone No.: (610) 428-2417
Location: Aura Laboratories, Inc.

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

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

MESSAGE CONFIRMATION

05/24/02 15:24
ID=DMEDP-CDER-FDA

NO.	MODE	BOX	GROUP
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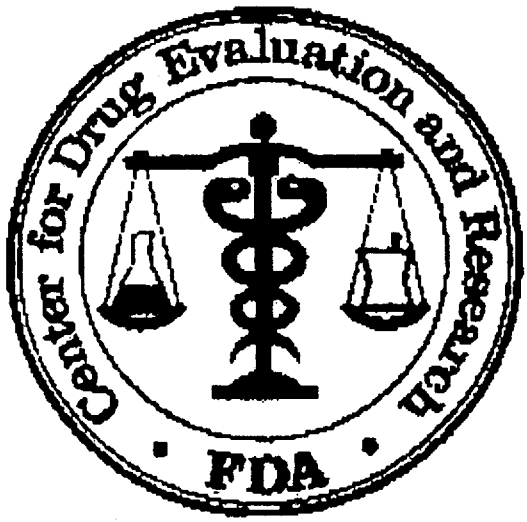
FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: May 24, 2002

APPEARS THIS WAY
ON ORIGINAL



Comments:
Attached is a copy of correspondence from the Division regarding NDA 21-316. The original letter will be sent by mail.

Don't hesitate to call with any questions.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
Andrx Laboratories, Inc.
401 Hackensack Avenue
Hackensack, NJ 07601

RE: NDA #21-316
Altocor™ (lovastatin) Extended Release Tablets
MACMIS ID # 10785

Dear Dr. Farina:

This letter responds to Andrx Laboratories, Inc.'s (Andrx) April 29, 2002 request to the Division of Drug Marketing, Advertising and Communications (DDMAC) for comments on proposed launch promotional materials for Altocor™ (lovastatin) Extended Release Tablets. The materials include two (2) sample boxes.

Comments on the initial sample boxes were provided under separate cover on April 12, 2002. DDMAC has reviewed your revised sample boxes and has the following comments. These comments are tentative and subject to change as they are based upon the draft product labeling (draft PI). These comments should apply to all current and future promotional materials for Altocor with the same or similar claims and presentations.

We remind you that the term "new" should only be used for six months after the date Altocor is initially marketed. After that six months, materials containing the term "new" should be revised or replaced.

If you have any questions or comments, please contact me by facsimile at (301) 594-6759, or in writing, at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

APPEARS THIS WAY
ON ORIGINAL

In all future correspondence regarding this particular matter, please refer to MACMIS ID #10785 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Cheryl D. Cropp, Pharm.D., BCPS
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

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/s/

Cheryl Cropp
5/17/02 02:37:15 PM

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DOCUMENT INFORMATION PAGE

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Application #(s):	21316
Document Type:	NDA Letters
Document Group:	DDMAC Staff Letters
Document Name:	10785 051702 ADLP
MACMIS #	10785
MACMIS Type Code	LETT
MACMIS Action Code	ADLP
Due Date	
Close Out	No
Admis #	
Admis Material ID	
FOI Status	NOT RELEASABLE-Launch
Drafted by/date:	Cropp 05.13.02
Comments by/date:	Chong 05.14.02; Chong 05.16.02
Consult by/date:	
Revised by/date:	Cropp 05.15.02; Cropp 05.17.02
Concurred by/date:	Chong 05.16.02
Finalized/date:	Cropp 05.17.02
Filename:	altocor[2].sample.boxes.05.13.02
DFS Key Words:	
Notes:	Altocor Launch Advisory for Revised Sample Boxes

END OF DOCUMENT INFORMATION PAGE

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-316

DISCIPLINE REVIEW LETTER

Aura Laboratories, Inc.
Attention: Nicholas J. Farina, Ph.D.
Vice President of Regulatory Affairs
401 Hackensack Avenue, 9th Floor
Hackensack, New Jersey 07601

Dear Dr. Farina:

Please refer to your March 30, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Altocor (lovastatin) Tablets.

Our review of the Biopharmaceutics section of your submission is complete, and we have identified the following deficiency:

The following dissolution method and specification is recommended:

Dissolution Method; USP apparatus 2 (paddle) at 50 rpm, medium (900 mL) of — sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5 and temperature 37°C. Dissolution specification;

Time (hr)	Amount Dissolved (%)
2	—
8	—
—	—

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
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Document Information Page

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Application #(s):	NDA 21-316
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Discipline Review letter for a pending NDA
Shortcut ID Code:	NDA-E2
COMIS Decision:	DR (DISCIPLINE REVIEW)
COMIS Data Entry:	
Drafted by:	WCK/January 9, 2002
Revised by:	HAhn01.09.02
Initialed by:	MParks01.09.02
Finalized:	WKoch01.09.02
Filename:	C:\WINDOWS\Desktop\NDA21316\LTRdrbph011002.doc
DFS Key Words:	
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END OF DOCUMENT INFORMATION PAGE

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

DATE: January 09, 2002

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ON ORIGINAL

Comments:

Attached is a copy of correspondence
from the Division regarding NDA 21-316.
The original letter will be sent by mail.

Please don't hesitate to call with any questions.

TO:
Name: Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
Fax No.: (201) 883-1893
Phone No.: (610) 428-2417
Location: Aura Laboratories, Inc.

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

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

MESSAGE CONFIRMATION

01/09/02 18:42
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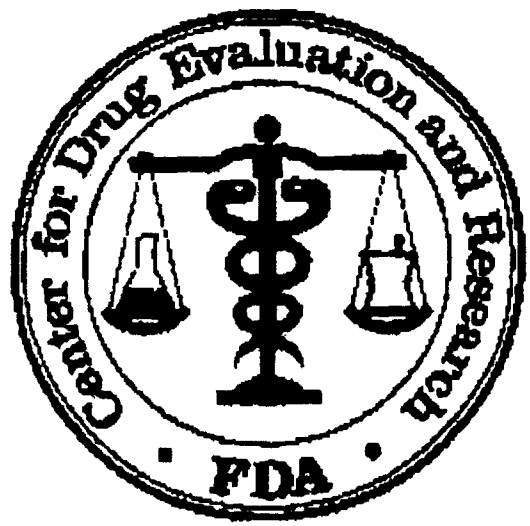
FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: January 09, 2002



APPEARS THIS WAY
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Comments:

Attached is a copy of correspondence from the Division regarding NDA 21-316. The original letter will be sent by mail.

Please don't hesitate to call with any questions

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-316

Aura Laboratories, Inc.
Attention: Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
401 Hackensack Avenue, 9th Floor
Hackensack, New Jersey 07601

Dear Dr. Farina:

Reference is made to your correspondence dated July 26, 2001, requesting FDA issue a Written Request under Section 505A of the Food, Drug, and Cosmetic Act for lovastatin modified-release tablets.

We have reviewed your proposed pediatric study request and are unable to issue a Written Request based on your submission.

The Agency has determined that until safety and effectiveness of the immediate-release formulation of lovastatin have been established in children and adolescents with heterozygous familial hypercholesterolemia, we cannot adequately assess the potential public health benefit in this population of treatment with the lovastatin modified-release formulation and thus the nature and extent of the clinical information that may be requested of you in order to obtain pediatric exclusivity.

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

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
1/2/02 03:05:20 PM

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DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	[redacted]
Document Type:	[redacted] letter
Document Group:	Pediatric Exclusivity/Rule Letters
Document Name:	Inadequate Proposed Pediatric Study Request
Shortcut ID Code:	[redacted]-PED-3
COMIS Decision:	DN: DENIED – INADEQUATE PEDIATRIC STUDY REQUEST
Drafted by:	WKoch12.10.01
Revised by:	DOrloff12.21.01/MParks01.02.02/APariser01.02.02
Initialed by:	
Finalized:	WKoch01.02.02
Filename:	C:/WINDOWS/DESKTOP/NDA21316/LTRwrDEN123101
DFS Key Words:	
Notes:	07.26.01
Linking Instructions:	Link this outgoing letter to all related IND and NDA incoming documents coded either PA (for the Proposed Pediatric Study Request) or PB (amendment to the Pediatric Written Request).

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-316

DISCIPLINE REVIEW LETTER

Aura Laboratories, Inc.
Attention: Nicholas J. Farina, Ph.D.
Vice President of Regulatory Affairs
401 Hackensack Avenue, 9th Floor
Hackensack, New Jersey 07601

Dear Dr. Farina:

Please refer to your March 30, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Altocor (lovastatin) Extended-Release Tablets, 10 mg, 20 mg, 40 mg, and 60 mg.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies:

1.

e

2.

WITHHOLD 2 PAGE (S)

9. Regarding the draft labeling:

(a) Revise the inactive ingredient list as follows:
1) revise "confectioner's sugar" to indicate the presence of "corn starch";
2) revise "synthetic iron oxides" to "synthetic black iron oxide" and "red iron oxide";
3) add "propylene glycol"; and
4) revise "PEGs" to "PEG 400" and "PEG 8000".

(b) Revise the proposed storage statement to use the USP definition of controlled room temperature (20-25°C) which is supported by the submitted stability studies.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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

Sincerely,

{See appended electronic signature page}

Stephen K. Moore, Ph.D.
Chemistry Team Leader I
Division of Metabolic
and Endocrine Drug Products, HFD-510
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

**APPEARS THIS WAY
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/s/

Stephen Moore
12/11/01 05:26:28 PM

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Document Information Page

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Application #(s):	NDA 21-316
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Discipline Review letter for a pending NDA
Shortcut ID Code:	NDA-E2
COMIS Decision:	DR (DISCIPLINE REVIEW LETTER)
COMIS Data Entry:	
Drafted by:	WKoch/12.11.01
Revised by:	EGalliers12.11.01
Initialed by:	
Finalized:	WKoch12.11.01
Filename:	C:\WINDOWS\DESKTOP\NDA21316\LTRirCMC121501.doc
DFS Key Words:	
Notes:	
Linking Instructions:	Link this letter to the incoming document containing the information requiring further clarification.

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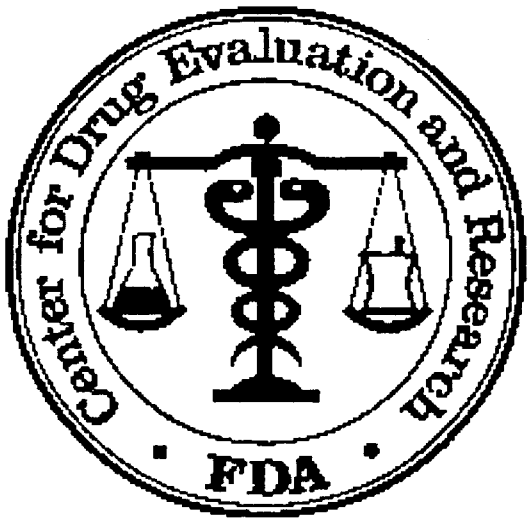
FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: December 12, 2001



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Comments:

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from the Division regarding NDA 21-316.
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Please don't hesitate to call with any questions.

TO:
Name: Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
Fax No.: (201) 883-1893
Phone No.: (610) 428-2417
Location: Aura Laboratories, Inc.

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

Pages (including this cover sheet): Seven (7)

MESSAGE CONFIRMATION

12/12/01 10:31
ID=DMEDP-CDER-FDA

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958	TX		

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

DATE: December 12, 2001

APPEARS THIS WAY ON ORIGINAL

Comments:
Attached is a copy of correspondence
from the Division regarding NDA 21-316.
The original letter will be sent by mail.

Please don't hesitate to call with any questions.

TO: **FROM:**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-316

INFORMATION REQUEST LETTER

Aura Laboratories, Inc.
Attention: Nicholas J. Farina, Ph.D.
Vice President of Regulatory Affairs
401 Hackensack Avenue, 9th Floor
Hackensack, New Jersey 07601

Dear Dr. Farina:

Please refer to your March 30, 2001, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ——— (lovastatin) Extended-Release Tablets, 10mg, 20mg, 40mg, and 60mg.

We are reviewing the Biopharmaceutical section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Formulations used in clinical trials

You have provided a summary of lovastatin formulations (page 60, VOL 15) as a percent weight (relative) of individual components. In addition, we are requesting the absolute values of those individual components.

2. Dissolution

You have provided one dissolution condition. In this regard, we would like to request a justification of that condition and related additional information including:

1) justification of concentration of ——— in dissolution medium,
2) comparison of paddle speed between 50 rpm and 75 rpm,
3) solubility in different pH media, and
4) dissolution profiles in different pH media.

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

Sincerely,

{See appended electronic signature page}

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

**APPEARS THIS WAY
ON ORIGINAL**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Enid Galliers
7/24/01 10:21:07 AM

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Document Information Page

This page is for FDA internal use only. **Do NOT send this page with the letter!**

Application #(s):	NDA 21-316
Document Type:	NDA Letter
Document Group:	Information Request Letters
Document Name:	Information request letter for a pending NDA
Shortcut ID Code:	NDA-E1
COMIS Decision:	IR (INFORMATION REQUEST)
COMIS Data Entry:	
Drafted by:	wck/July 20, 2001
Revised by:	HAhn07.23.01/EGalliers07.23.01
Initialed by:	
Finalized:	WKoch07.24.01
Filename:	C:\WINDOWS\DESKTOP\NDA21316\LTRir072301.doc
DFS Key Words:	
Notes:	
Linking Instructions:	Link this letter to the incoming document containing the information requiring further clarification.

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-316

Aura Laboratories, Inc.
Attention: Nicholas J. Farina, Ph.D.
Vice President, Regulatory Affairs
401 Hackensack Avenue, 9th Fl
Hackensack, NJ 07601

Dear Dr. Farina:

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: ———— lovastatin extended-release) Tablets, 10, 20, 40, 60 mg

Review Priority Classification: Standard (S)

Date of Application: March 30, 2001

Date of Receipt: March 30, 2001

Our Reference Number: NDA 21-316

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 May 29, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 30, 2002, and the secondary user fee goal date will be March 30, 2002.

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, 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 approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

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 make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans

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 review your pediatric drug development plan and notify you of its adequacy. 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, call me at (301) 827-6411.

Sincerely,

{See appended electronic signature page}

Margaret Simoneau, R.Ph.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Margaret Simoneau
4/5/01 12:56:05 PM

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Document Information Page

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	NDA 21-316
Document Type:	NDA Letter
Document Group:	Acknowledgement Letters
Document Name:	NDA Acknowledgement Letter
Letter Code:	NDA-A1
COMIS Decision:	No Decision Code (*ACKNOWLEDGEMENT*)
Drafted by:	ddk/April 4, 2001
Revised by:	Keels/April 4, 2001
Initialed by:	Simoneau 4.4.01/Galliers 4.4.01
Finalized:	Ddk/April 4, 2001
Filename:	21316AC.DOC
DFS Key Words:	
Notes:	
Linking Instructions:	Link the outgoing letter to the original N 000 incoming document for the NDA.

END OF DOCUMENT INFORMATION PAGE

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Meeting Minutes

Division of Metabolic and Endocrine Drug Products
NDA 21-316

Date: Friday, May 18, 2001
Location: Parklawn 14B45

Time: 9:30 to 10 AM

FDA Attendees:
Dr. Parks, Dr. Pariser, Hae-Young Ahn, Sang Chung, Indra Antonipillai, Stephen Moore, Joy Mele and M. Simoneau.

This was a **Filing meeting** for NDA 21-316, —— (lovastatin extended-release) 10, 20, 40, and 60 mg tablets, submitted March 30, 2001, received March 30, 2001. This NDA is for the treatment of hyperlipidemia.

- **Clinical**- Dr. Pariser is the primary medical reviewer. There were no filing issues and the financial disclosure was submitted.
- **Pharmacology**- no filing issues.
- **Chemistry**- no filing issues.
- **Biopharm**- no filing issues.
- **Biostatistics**-no filing issues.
- **DSI**- An audit will be requested.
- **Advisory Committee**- not needed.
- **Review Goal Date with labeling**-
  This submission will be a standard review. The primary user fee goal date is January 30, 2002. Primary reviews are due December 15, 2001.

  Post Meeting Notes:

1. Dr. Farina was contacted after the filing meeting and notified that the submission would be on a standard review. At this time, I was notified that another trade name would be submitted to the Agency. OPDRA will receive the ***new*** trade name consult when there is an official submission.
2. ( )

Minutes preparer: M. Simoneau (*See appended signature page*)

Concurrence Chairman: Dr. Parks (*See appended signature page*)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mary Parks
6/25/01 02:00:39 PM

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ON ORIGINAL

Meeting Minutes

Division of Metabolic and Endocrine Drug Products
IND—— Lovastatin Extended Release Tablets

Date: Wednesday, December 9, 1998
Location: Parklawn, Third Floor, Conference Room "Q"
Time: 9:30-10:30AM

FDA and Aura Laboratories, Inc. Attendees:
See enclosure 1

1. Meeting Objective

This was a End of Phase II meeting requested by Aura Labs. Enclosure 2 is the October 22, 1998 fax requesting this meeting. A briefing package was submitted to the IND on November 27, 1998. Within this November 25, 1998 submission, on page 43, "number 10. Items for Discussion" (enclosure 3) were the discussion points.

2. Discussion and Conclusions

The items discussed and their resolutions are listed in enclosure 4, fax dated December 16, 1998. This fax was reviewed by all FDA members present with a date correction to be December 9, 1998 and no other additional corrections or notations.

Minutes preparer: M. Simoneau /S/ 12/23/98

Concurrence Chariman: D. Orloff /S/ 1/7/99

cc: IND ——
DivFile
Aura fax 12.16.98 initialed by:
MParks12.18.98/JMele12.17.98/HAhn12.18.98/JWei12.18.98/RSteigerwalt12.16.98

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WITHHOLD 7 PAGE (S)

Draft

NO ADVISORY COMMITTEE MEETING

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Electronic Mail Message

Date: 7/3/01 1:14:12 PM
From: Sammie Beam 301-827-3231 FAX 3 (BEAMS@A1)
To: WILLIAM C KOCH JR (FDACD) (KOCHW@A1)
Subject: OPDRA consult #01-0148 for NDA 21-316

Hello,

The above consult number has been assigned for the changed proposed proprietary name review for the indicated application.

Thanks,
Sammie Beam

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ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office) HFD-400 Attn: Sammie Beam			FROM: HFD-510	
DATE June 26, 2001	IND NO. NA	NDA NO. 21-316	TYPE OF DOCUMENT New Drug Application	DATE OF DOCUMENT June 8, 2001
NAME OF DRUG (lovastatin extended release tablet)		PRIORITY Standard	CLASSIFICATION OF DRUG Lipid Altering	DESIRED COMPLETION DATE November 1, 2001

NAME OF FIRM: Aura Laboratories Inc.

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the attached letter and package insert.
Sharon Kelly, Ph.D. is the reviewing chemist, (301) 827-6394.
William C. Koch, R.Ph., Regulatory Project Manager, (301) 827-6412.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)* MAIL XHANDX
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Consult.088

Team Leader Concurrence: _____
Date

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/s/

Stephen Moore
6/26/01 03:40:11 PM

Document Information Page

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Application #(s):	NDA 21-316
Document Type:	FORMS
COMIS Decision:	
Drafted by:	WKoch/06.26.01
Revised by:	
Initialed by:	
Finalized:	WKoch/ .00
Filename:	C:/Windows/Desktop/NDA 21316/CONopdra062601.doc
DFS Key Words:	
Notes:	06.08.01
Linking Instructions:	

END OF DOCUMENT INFORMATION PAGE

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ORIGINAL

Aura
LABORATORIES, INC.

June 8, 2001

N 000 C

NEW CORRESP

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

Subject: NDA-316 21316
Lovastatin Extended Release Tablets
General Amendment to a Pending Application

Dear Sir:

Our NDA for Lovastatin Extended Release Tablets was submitted to your Division on March 30, 2001 and was filed on May 29, 2001. In our original submission, we submitted the tradename — for our product. We are hereby notifying you that we want to change the trademark of — to Altocor.

We are confident that Altocor is an appropriate name for our controlled-release formulation, Lovastatin Extended Release Tablets.

If you have any questions, please contact me anytime at 610-428-2417.

Sincerely,

Nicholas J. Farina, PhD
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

401 Hackensack Avenue • 9th Floor • Hackensack, New Jersey 07601

AN
ANDRX COMPANY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-400 ODRA
C. Sammie BEAM Rm-15B03

FROM: HFD-510 METABOLIC AND ENDOCRINE DRUG PRODUCTS

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/12/01			Request for FDA Comment	JANUARY 8, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Tablets LOVASTATIN EXTENDED RELEASE	NDA Submission in MARCH 2001	Lipid Altering	FEBRUARY 28, 2001

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the enclosed Submission (6 copies).
If there are any questions please contact:
Chemist - Sharon Kelly, PhD (301-76394
Project Manager - Margaret Sansoucie 7-6411

SIGNATURE OF REQUESTER: /S/

METHOD OF DELIVERY (Check one) ☐ MAIL ☒ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Chemistry Team Leader /S/ 1/11/01

January 8, 2001

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

Subject: IND ———
Lovastatin Extended Release Tablets
General Correspondence
Serial No.: 042

Dear Sir:

Aura Laboratories, a division of Andrx Corporation, has developed a lovastatin extended release tablet. The product is formulated for a once-a-day administration. This new formulation will be marketed in 10, 20, 40 and 60 mg tablets. This product will be targeted for the treatment of hypercholesterolemia. Our current plan is to submit our ——— Lovastatin) NDA to your Division in March of this year.

We request a review of the tradename — by the FDA/Office of Postmarketing Drug Risk Assessment (OPDRA) for approval. A market research package prepared by the ——— is also enclosed with data supporting the selection of the trade name. (We have enclosed ten copies.)

The ——— specializes in developing and researching of pharmaceutical and biologic brand names. The research methodology used by the ——— includes practitioner review of nomenclature to identify potential confusion in the prescribing chain that may result in patient harm.

The market research conducted by the ——— has been submitted to the FDA several times since 1997 regarding nomenclature issues and their research methodology has been continually updated in response to NDA nomenclature concerns. Most recently, the ——— updated the methodology after meeting with the FDA/OPDRA on April 22, 1999 to include measurement of sound-alike and look-alike potential confusion, positive and negative control names and simulation of real-world prescribing and dispensing environment.

In summary, the ——— research found the following regarding the tradename ———

- Pharmacists' verbatim unaided interpretation of physicians' verbal and written prescription resulted in insignificant confusion with currently marketed brand and generic drugs.

- Unaided responses from both physicians and pharmacists indicated insignificant "Sound-Alike" or Look-Alike" potential confusion with currently marketed drugs.

- The comprehensive safety evaluation revealed an insignificant number of marketed brand name citations, with no potential for patient harm.

- An evaluation of —— by pharmacists for dispensing accuracy resulted in 100% overall accuracy in dispensing.

- An advisory panel from the ——————————— and ——————— confirmed that there were insignificant patient harm issues for —— and current brand and/or generic drugs.

The attached report reviews these conclusions in detail and sets forth the methodology relied upon by ——— We are confident that the attached patient safety research and conclusions support that —— is an appropriate name for the controlled-release formulation of ———Lovastatin Extended Release Tablets).

Please be advised if you have any questions, please contact me anytime at 610-428-2417.

Sincerely,

Nicholas J. Farina, PhD
Vice President, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL