CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-316

PHARMACOLOGY REVIEW(S)

NDA 21-316

Signed off in DFS on 10/4/01
Review completed: September 17, 2001

Sponsor: Aura Laboratories, Inc.; Hackensack, NJ, 07601.

Date Submitted: March 30, 2001.

Date Received: April 2, 2001.

Drug Class: Statin

Category: Cholesterol lowering agent

Indication: To lower lipids.

Indra Antonipillai, Ph.D.

cc: NDA Arch
HFD-510
HFD-510/davisbruno/antonipillai/pariser/simoneau
File Name nda21316, lovastatin XL, Review # 1
Safety code: AP

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ON ORIGINAL

NDA 21-316

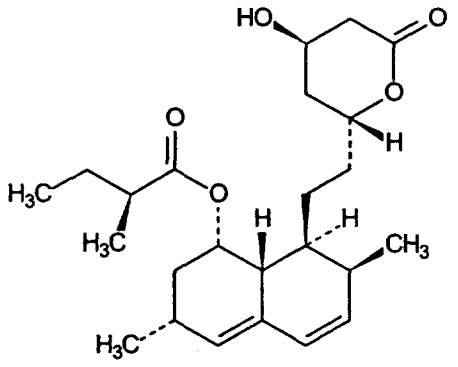
REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS: Statins, lipid, cholesterol, heart, dyslipidemia
Reviewer Name: Indra Antonipillai
Division Name: Division of Metabolic and Endocrine Drug products.
HFD# 510
Review Completion Date: 9/17/2001

IND/NDA number: NDA 21-316.
Serial number/date/type of submission: March 30, 2001, original submission #000.
Information to Sponsor: Yes ( ) No (X) - (labeling)
Sponsor or agent: Aura Laboratories, Inc.; Hackensack, NJ, 07601.

Drug:
Name: Lovastatin extended release tablets (lovastatin XL)
Trade Name: ———.
Generic Name: Lovastatin (Mevacor, ———————).
CAS Registry Number (if provided by sponsor): N/A
Chemical Name: 1S-1α®, 3α, 7β, 8β, (2S, 4S), 8αβ)-1,2,3, 7, 8,a-hexahydro-3,7-dimethyl-8-(2-tetra-hydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl)-1-napthalenyl-,2-methylbutanoate. The current drug product is an extended release formulation of lovastatin. The formulation consists of an ———————

Molecular Formula/ Molecular Weight: $C_{24}H_{36}O_5$/ MW 404.55;
Structure:



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Relevant INDs/NDAs/DMFs:
NDA 19-643 (Lovastatin, Merck Sharp and Dohme)
IND — (Aura Laboratories, Inc.)
IND —
DMF ———————

Drug Class: Cholesterol lowering agent, an HMG-CoA reductase Inhibitor.

Indication: Treatment of hypercholesterolemia.

Clinical formulation (and components): 10, 20, 40 and 60 mg white tablets once/day doses are proposed for the commercial use. The tablet consists of an ——— ——— and ——— Core contains active drug substance, ——— Exciepients are all commonly used pharmaceutical ingredients. Most are USP/NF compendial-grade. The tablets also contain the following inactive ingredients: acetyltributyl citrate, cellulose acetate, butylated hydroxyanisole, candellila wax, cellulose acetate, confectioners' sugar; F D & C yellow # 6; glyceryl monostearate, hydroxypropyl methylcellulose; hypromellose phthalate, lactose, methacrylic acid copolymer, type B; polyethylene glycol, polyethylene oxides, polysorbate 80; silicon dioxide, sodium chloride, sodium lauryl sulfate, synthetic iron oxides; talc; titaneum dioxide and triacetin. See appendix 1, Table 1

Route of administration: oral

Proposed Indication: —— extended release tablets are indicated for the treatment of dyslipidemia, and in —— prevention of atherosclerotic vascular disease. The drug should be used as an adjunct to diet for reduction of elevated total and LDL-cholesterol

Introduction and drug history:

The drug —— ontains an extended-release form of lovastatin (an HMG-CoA reductase inhibitor). Lovastatin is a cholesterol lowering agent, currently marketed drug in USA. The initial NDA (NDA 19-643) for lovastatin was approved on 8/31/1987 at recommended doses of 10, 20, 40 and 80 mg/day.

Studies reviewed within this submission: Since most of the preclinical pharmacology/toxicity studies were submitted in the original application of lovastatin (NDA 19-643), no new pharm/tox studies were submitted here to support the use of this drug. Sponsor had submitted one 3-month pilot toxicity/TK study under the IND —— for this drug, and the review of this IND is included in appendix 2 (review # 2). However, TK data on a pilot dog study were not provided previously, and are provided in the current NDA submission.

Toxicokinetic Data on a Three Month Oral Gastrointestinal Toxicity Study in beagle Dogs With Lovastatin XL (Study No: TX-146-01):

The complete toxicity review on this dog study is included under IND —— in appendix 2, review # 2. This study showed some clinical signs in dogs, indicating a relationship between treatment with the drug and the occurrence of soft/mucoid feces, particularly in male dogs. There was a definite increase in these findings in drug treated male animals

compared to controls, at approximately 8-times the human dose of 60 mg/day based on body surface area. Data shown are # of occurrences / # of dogs in Table 1.

Table 1: Soft/mucoid feces in 3-month toxicity study in dogs

Finding	Control	160 mg
MALES		
Soft stools	0/0	46/5
Mucoid stools	23/4	54/7
FEMALES		
Soft stools	19/5	11/5
Mucoid stools	27/5	28/5

The TK data in the above 3-month dog study (in the current submission) were as follows: The AUC values in females were 1.3 to 1.5 times higher (day 1: 1537 ng.eq.hr/ml) than in males (1016 ng.eq.hr/ml). Sponsor states that females may have received higher amounts of the drug due to their smaller size. Maximum plasma conc. were achieved within 3.5-5 hrs, and half-life of the drug was 4-5 hrs. The drug did not accumulate over time ($AUC_{0\text{-}24\ hr}$ values in M+F dogs on **day 1**: 1276 ng.eq.hr/ml, **day 86:** 1235 ng.eq.hr/ml). See appendix 1, Table 2.

OVERALL SUMMARY AND EVALUATION:

Introduction: The drug lovastatin is a cholesterol-lowering drug; it is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme that catalyzes the rate-limiting step in cholesterol synthesis. Lovastain has been marketed extensively by Merck for many years (NDA 19-643, approved on 8/31/1987), for oral administration under the trade name Mevacor. The current sponsor has now come up with the new extended release formulation of lovastatin (lovastatin XL, ——, which they claim enhances the activity of the compound to provide even greater reduction of blood serum cholesterol.

The current tablet consists of an ——— and a ———— ——— Core contains active drug substance, ———— This product is an alkyl ester of a hydroxy substituted naphthalene derivative, it provides a slow controlled release of the compound, with more constantly bioavailable drug and lower peak plasma conc. The formulation is based on an —— dosage, which is designed to ———— The —— consists of a ———— in a ———— This formulation supposedly provides enhanced effect vs the conventional immediate release Mevacor.

—— is indicated for the treatment of primary hypercholesterolemia, dyslipidemia, and in —— prevention of atherosclerotic vascular disease. The proposed doses of —— (10-60 mg/day) that are going to be marketed are lower than the currently marketed doses of Mevacor (10-80 mg/day).

Safety Evaluation: There are no preclinical safety studies submitted with this NDA, except a pilot 3-month toxicity/TK study of the drug in dogs to examine the GI toxicity. This toxicity study in dogs used only one dose of the drug (160 mg/dog), and the clinical formulation used at that time in dogs appears slightly different than the current clinical formulation. The drug produced clinical signs (soft/mucoid stools, see Table 1) in male dogs, at approximately 8-times the human dose of 60 mg/day, based on body surface area. No other GI toxicity, including changes in histopathology in the GI tract of animals was observed. In clinical studies, —— also produces some GI or abdominal toxicity in humans, including diarrhea, dyspepsia, flatulence and nausea.

The NOEL doses of Mevacor (lovastatin from NDA 19-643) in rats and dogs were 30 mg/kg/day. The safety factor (at approved 80 mg/day human dose of mevacor) in rats was 3-fold and in dogs was 12-fold.

The current product has Tmax of — hrs vs it is —hrs for mevacor, so there is a possibility that this drug can accumulate. However in a 3-month dog toxicity and TK study the current drug did not accumulate at the end of 3-months. The sponsor did not compare the half life of lovastatin XL vs mevacor in the dog study

As for general pharm/tox information is concerned, the carcinogenicity, mutagenicity or impairment of fertility studies with — have not been conducted. However, sponsor has provided the summary of available pharmacology and toxicity studies on lovastatin from the published literature and from NDA review. The toxicities with lovastatin (Mevacor) are well characterized and there is considerable experience with the drug.

Carcinogenicity, mutagenicity or impairment of fertility and repro-tox studies conducted with lovastatin are indicated under the label for lovastatin (in —— label). Lovastatin carcinogenicity studies have indicated increased incidence of hepatocelluar carcinomas and adenomas, pulmonary adenomas, papilloma of non-glandular stomach mucosa, and thyroid neoplasm. Lovastatin is not mutagenic, and has a pregnancy category 'X' in the label. Thus the proposed labeling text under these headings is what is reported under labeling for Lovastatin

Labeling Review: In general, no new preclinical sections of label for —— have been provided. The label for —— basically includes approved label from Mevacor (lovastatin). However, the following changes in labeling are recommended:

1.Under the heading 'Pregnancy and lactation'

Internal comments: Since lovastatin is an approved drug, its safety profile has been well characterized, and is used at approved doses, the approval (AP) of the current application of — is recommended, pending labeling changes.

External Recommendation: From the preclinical standpoint, approval of this application is recommended, pending labeling changes. The reviewer also recommends deleting a ——— included in the label under the ——— section (in section 3, page 42) from the label.

Indra Antonipillai, Ph.D.
Pharmacologist, HFD-510

cc: NDA Arch
HFD510
HFD510/antonipillai/davisbruno/pariser/simoneau
Filename: nda21312

Appendix 1, Table 1:
Clinical formulation and components of [redacted]

The composition of the four tablet strengths is as follows:

Unit Dose Composition of Lovastatin XL Tablets (mg)

Components	Tablet Strength (mg/tablet)			
	10 mg	20 mg	40 mg	60 mg
Lovastatin, USP [redacted]	10.00	20.00	40.00	[redacted]
[redacted] Lactose, NF	[redacted]			
Polyethylene Oxide, NF [redacted]				
Sodium Lauryl Sulfate, NF				
Butylated Hydroxyanisole, NF				
Polyethylene Oxide, NF [redacted]				
[redacted] Silicon Dioxide, NF				
Glyceryl Monostearate, NF				
[redacted]				
Sodium Chloride, USP [redacted]				
Hydroxypropyl Methylcellulose [redacted]				
[redacted]				
Talc, USP				
Acetyltributyl Citrate, [redacted]				
Sugar, Confectioner's [redacted]				
Cellulose Acetate, [redacted]				
Methacrylic Acid Copolymer, NF, Type B [redacted]				
Triacetin, USP				
Polyethylene Glycol 400, NF				
[redacted]				
Candelilla Wax [redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
Total	**169.56**	**169.56**	**337.06**	**333.58**

[redacted]

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Appendix 1, Table 2:

Toxicokinetic Data on a Three-Month Oral Gastrointestinal Toxicity Study in beagle Dogs With Lovastatin XL (Study No: TX-146-01):

Mean (± SD) Toxicokinetic Parameter Values Following Oral Administration of Lovastatin XL to Beagle Dogs for 3 Months

Study Day	Sex	C_{max} (ng eq/ml)	T_{max} (hr)	$AUC_{0\text{-}24\ hr}$ (ng eq•hr/ml)	$AUC_{0\text{-}\infty}$ (ng eq•hr/ml)	$t_{1/2}$ (hr)[a]
1	Male	175.5 ± 96.5	3.5 ± 0.9	1,016 ± 398	1,088 ± 418	5.2
	Female	228.7 ± 186.3	3.8 ± 0.7	1,537 ± 586	1,690 ± 644	4.5
	Combined	202.1 ± 146.0	3.6 ± 0.8	1,276 ± 554	1,366 ± 598	4.8
86	Male	143.3 ± 72.9	3.8 ± 3.5	1,213 ± 920	NR	3.6
	Female	154.5 ± 55.7	5.0 ± 7.7	1,256 ± 391	NR	4.9
	Combined	148.9 ± 63.0	4.4 ± 5.8	1,235 ± 683	NR	4.2

[a]Harmonic mean.
NR = Not reported.

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Appendix 2: Review # 1: IND —— (June 16, 1997 submission)

PROJECT MANAGER NOTE: ITEMS TO BE COMMUNICATED TO SPONSOR

IND —— **Review Completed:**
June 24, 1997

Sponsor: Aura Laboratories, Inc.; Fort Lauderdale, FL 33314

Date Submitted: June 11, 1997 **Date Received:** June 16, 1997

PHARMACOLOGY REVIEW OF INITIAL IND SUBMISSION
IND —— Serial #000 (June 16,1997)

DRUG: Lovastatin E-R (XL) tablets

STRUCTURAL FORMULA:

FORMULATION: White tablet consisting of an —— and a —— Core contains active drug substance, —— —— Excipients are all commonly-used pharmaceutical ingredients. Most are USP/NF compendial-grade. (acetyltributyl citrate, cellulose acetate, glyceryl monostearate, hydroxypropyl methylcellulose —— lactose, methacrylic acid copolymer, —— polyethylene glycol 400, poly (ethylene oxide), silicon dioxide —— sodium chloride, sodium lauryl sulfate, sugar, talc and triacetin). Proposed tablet function similar to —— formulations.

CATEGORY: Cholesterol-lowering agent

INDICATION: Not specified

RELATED NDA/DMF: DMF ——, NDA 19-643 (mevacor; Merck SBOA)

CLINICAL STATUS: Phase I/II: Phase I studies will be in healthy subjects.
Crossover Single-dose PK to evaluate the safety and PK profiles of Lovastatin XL relative to Mevacor® (40 mg each drug). N=8
Crossover multiple-dose (7 days) PK study to compare the safety and steady state PK of Lovastatin XL relative to Mevacor® (40 mg each drug) N=12
A single dose three-way crossover oral dose proportionality study to examine kinetic linearity of lovastatin over the dose range of **40-120 mg** of lovastatin XL. N=12.
3-way crossover single-dose Bioavailability study of final market-composition Lovastatin XL relative to Mevacor®. Also, food effect on rate and extent of absorption of Lovastatin XL. (40 mg each drug)
Phase II: Dose response in patients with primary hypercholesterolemia. Doses to be determined. Comparison to Mevacor®. Daily dosing for 4 weeks 20 patients/group).

ANTICIPATED SPECIAL RISKS: There has been considerable experience with MEVACOR® and toxicities are well-characterized. It is not expected that any additional systemic toxicities will be encountered, particularly since overall C_{max} levels are expected to be lower than with MEVACOR®. However, the formulation is similar to the — formulations of — currently under investigation and like the — formulations, the possibility of G.I. toxicity with the extended release formulation should be addressed.

PHARMACOLOGY COMMENTS: No new pharmacology data were provided. It is not expected that any additional systemic toxicities other than those already known for lovastatin will be encountered, particularly since overall C_{max} levels are expected to be lower than with MEVACOR®. The sponsor does not intend to submit any new nonclinical studies and proposes to rely on the agency SBOA for MEVACOR® for nonclinical data. However, with similar preparations — for other — the possibility of G.I. irritation was raised. The sponsor for those preparations — performed (or is performing) G.I. irritation studies in dogs. Daily dosing of appropriate multiples of the — for 3 months was recommended by the agency. (I might also note that — had initiated studies with — Given the similarity of the XL formulation and the — formulations, it seems reasonable to request studies to assess potential G.I. toxicity for this preparation.

PHARMACOLOGY RECOMMENDATION: The proposed studies may proceed. However, the dog g.i. study should be completed prior to the initiation of extended length clinical trials.

TO BE COMMUNICATED TO SPONSOR

Although systemic effects of lovastatin have been well-characterized, the extended gastrointestinal exposure with this formulation could result in g.i. toxicity which has not been characterized with MEVACOR®. The proposed studies may proceed. However, prior to the initiation of extended length clinical studies, we recommend a toxicology study in dogs to address this issue. This study should consist of daily dosing of appropriate multiples of the extended release formulation (preferably the formulation that will be marketed or one that has similar absorption characteristics) for three months. Any gross lesions of the g.i. tract noted at necropsy should be processed. In addition, sections from the esophagus, body and pyloric region of the stomach, duodenum, jejunum, ileum (including Peyer's patches), cecum and colon should be examined. PK analysis performed during this study would provide useful information for comparison to the approved Mevacor® formulation.

Ronald W. Steigerwalt, Ph.D.

cc: IND Arch
HFD510
HFD510/Orloff/Steigerwalt/Simoneau

Appendix 2: Review # 2: IND ——— (December 2, 1998 submission)

IND——— **Review Completed: March 19, 1999**

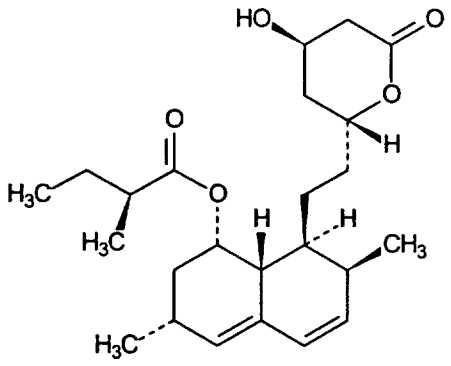
Sponsor: Aura Laboratories, Inc.; Fort Lauderdale, FL 33314

Date Submitted: November 30, 1998 **Date Received:** December 2, 1998

PHARMACOLOGY REVIEW OF INITIAL IND SUBMISSION
IND ——— Serial #015 (December 2,1998)

DRUG: Lovastatin E-R (XL) tablets

STRUCTURAL FORMULA:



CATEGORY: Cholesterol-lowering agent

INDICATION: Cholesterol lowering

RELATED NDA/DMF: DMF ———NDA 19-643 (mevacor; Merck SBOA)

CLINICAL STATUS: Phase I/II: Phase I studies will be in healthy subjects.

1. Crossover Single-dose PK to evaluate the safety and PK profiles of Lovastatin XL relative to Mevacor® (40 mg each drug). N=8
2. Crossover multiple-dose (7 days) PK study to compare the safety and steady state PK of Lovastatin XL relative to Mevacor® (40 mg each drug) N=12
3. A single dose three-way crossover oral dose proportionality study to examine kinetic linearity of lovastatin over the dose range of **40-120 mg** of lovastatin XL. N=12.
4. 3-way crossover single-dose Bioavailability study of final market-composition Lovastatin XL relative to Mevacor®. Also, food effect on rate and extent of absorption of Lovastatin XL. (40 mg each drug)

5. Phase II: Dose response in patients with primary hypercholesterolemia. Doses to be determined. Comparison to Mevacor®. Daily dosing for 4 weeks 20 patients/group).

ANTICIPATED SPECIAL RISKS: There has been considerable experience with MEVACOR® and toxicities are well-characterized. It is not expected that any additional systemic toxicities will be encountered, particularly since overall C_{max} levels are expected to be lower than with MEVACOR®. However, the formulation is similar to the — formulations of — currently under investigation and like the — formulations, the possibility of G.I. toxicity with the extended release formulation should be addressed.

TOXICOLOGY:

General Comments: A dog toxicology study with specific reference to g.i. toxicity was requested of the sponsor in the review of the initial submission to this IND. The sponsor provides the final report in this submission. The objective of this study was primarily to determine the potential local gastrointestinal toxicity of a long acting formulation. Only one dose group was used which tested exposures approximately 4 times the expected human exposure based on local g.i. exposure.

Study Title: A Three Month Oral Gastrointestinal Toxicity Study in beagle Dogs With Lovastatin XL (final report)
Study No: 3457.1 (— #), TX-146-01 (Aura #)
Amendment #015, Vol #1, and page # 002
Conducting laboratory and location: ———————————

Date of study initiation: July 9, 1998
GLP compliance: Yes
QA- Report Yes (X) No ()

METHODS:
Dosing: Clinical tablet formulation was tested at 4 tablets/dog (160 mg total dose).
species/strain: Beagle dogs.
#/sex/group or time point: 5/sex in control group. 8/sex in 160 mg dose group. Numbers were selected to provide 80% power using a one-sided nonparametric tolerance limit.
age: ~6 months
weight: 9.4-11.3 kg males and 7.8-9.4 kg females.
dosage groups in administered units: control and 160 mg (4 tablets of clinical formulation).
route, form, volume, and infusion rate: Orally administered tablets of clinical formulation.

Drug, lot#, radiolabel, and % purity: Lovastatin XL tablets ———————

Formulation/vehicle: White tablet consisting of an ——————— and a ——————— . Core contains active drug substance, ——————— Excipients are all commonly-used pharmaceutical ingredients. Most are USP/NF compendial-grade. (acetyltributyl citrate, cellulose acetate, glyceryl monostearate, hydroxypropyl methylcellulose ——— lactose, methacrylic acid copolymer, ——— polyethylene glycol 400, poly (ethylene oxide), silicon dioxide — sodium chloride, sodium lauryl sulfate, sugar, talc and triacetin). Proposed tablet function similar to — formulations.

OBSERVATIONS AND TIMES:
Clinical signs: general health/mortality: twice daily. Detailed clinical observations weekly.
Body weights: Prior to initiation then weekly
Food consumption: daily for days –6 to –1, then day1 to euthanasia. Reported as g/animal/day
Gross pathology: Terminal. Complete gross examination performed.
Histopathology: Terminal. GI tissues only: see histopath table.
Toxicokinetics: prior to dosing, then at 2, 4, 8, 12 and 24 h following dosing on day 1 and 86.

RESULTS:
Clinical signs: No mortality. Sponsor suggests no treatment-related observations. However, there did appear to be a relationship between treatment with drug and the occurrence of soft and mucoid feces particularly in male dogs. While these are common findings in dogs under laboratory conditions, there was a definite increase in these findings in treated male animals compared to controls. Data shown are # occurrences/# dogs

Finding	Control	160 mg
MALES		
Soft stools	0/0	46/5
Mucoid stools	23/4	54/7
FEMALES		
Soft stools	19/5	11/5
Mucoid stools	27/5	28/5

Body weights: Transient differences in body weights were not clearly dose related. Treated males tended to weigh less than controls.

Food consumption: No consistent dose related observations.

Gross pathology: No treatment-related effects.

Histopathology: No treatment-related effects.

Toxicokinetics: Data not provided in this report.

KEY STUDY FINDINGS:

There were no effects of the long acting Lovastatin XL tablet preparation that would indicate any significant gastrointestinal toxicity under the conditions of this study. If the occurrence in males of soft and mucoid feces is related to treatment, this is likely to be detectable in clinical trials, but does not seem to result in histopathological changes. No further action is necessary at this time.

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

cc: IND Arch
HFD510
HFD510//Steigerwalt/Simoneau
Review code: ND

Addendum 1:**Histopathology Inventory for IND** [redacted]

Study	TX-146-01
Species	Beagle
Adrenals	
Aorta	
Bone Marrow smear	
Bone (femur)	
Brain	
Cecum	X*
Cervix	
Colon	X*
Duodenum	X*
Epididymis	
Esophagus	X*
Eye	
Fallopian tube	
Gall bladder	
Gross lesions	
Harderian gland	
Heart	
Hyphophysis	
Ileum	X*
Injection site	
Jejunum	X*
Kidneys	
Lachrymal gland	
Larynx	
Liver	
Lungs	
Lymph nodes, cervical	
Lymph nodes mandibular	
Lymph nodes, mesenteric	
Mammary Gland	
Nasal cavity	
Optic nerves	
Ovaries	
Pancreas	
Parathyroid	
Peripheral nerve	
Pharynx	
Pituitary	
Prostate	
Rectum	
Salivary gland	
Sciatic nerve	
Seminal vesicles	
Skeletal muscle	
Skin	
Spinal cord	
Spleen	
Sternum	
Stomach	X*
Testes	
Thymus	
Thyroid	
Tongue	
Trachea	

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Urinary bladder	
Uterus	
Vagina	
Zymbal gland	

- organ examined
- histopathologically

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NDA 21-316 **1/11/02**

Addendum to Pharmacologist's labeling review of NDA 21-316

Following pharm/tox changes in the label were communicated to the sponsor on 12/20/01:

Labeling Review: Following changes in the label are recommended for NDA 21-316

*1. **Under the heading 'CNS Toxicity'***

Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) 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 for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS 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.

Justification for the changes: Above CNS toxicity appears verbatim in the Mevacor label. Sponsor has not submitted any data to justify its removal from the ALTOCOR label.

*2. **Under the heading 'Carcinogenesis, Mutagenesis, Impairment of Fertility'***

[redacted] In a 21-month carcinogenic study in mice with lovastatin, immediate-release there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas 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 lovastatin immediate-release 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 immediate-release].

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 given lovastatin immediate-release. 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 lovastatin immediate-release (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 of lovastatin immediate-release. 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.

[redacted] No evidence of mutagenicity was observed with lovastatin in a microbial mutagen 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.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day of lovastatin immediate-release. 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.

3. **Under the heading**

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4. **Under the heading 'Pregnancy'**

Pregnancy Category X

See CONTRAINDICATIONS.

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/m^2 surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either 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 of lovastatin immediate-release).

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 immediate-release 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 ALTOCOR™ during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. ALTOCOR™ 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 hazard.

Aura Laboratories's response:

As indicated earlier, the above labeling changes were sent to the sponsor on 12/20/01. On 1/4/2002, Aura Laboratories responded by suggesting that following statement be removed from the pharm/tox carcinogenicity albeling section (and similarly from the fertility and mutagenicity sections in the label)

[redacted]

The sponsor states that another HMG-CoA inhibitor, such as extended-release form Lescol XL does not have that statement. They have also given other examples such as glucophage XR, cardizem CD, procardia XL, and [redacted]

Since the current sponsor's (Aura Laboratories) application is 505(b)2, we wanted to clearly identify that studies were performed by the innovator, and not by the 505(b)2 sponsor. However, at this time there is no Center policy on this issue and labeling for 505(b)2 is case by case, **therefore, we will allow the sponsor to remove the above statements from the label.** However, the innovator's studies should be indicated as being performed with lovastatin

immediate release to accurately reflect the data, since Altocor has not been tested.

Following is the final pharm/tox label

*1. **Under the heading 'CNS Toxicity'***

Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) 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 for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS 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.

Justification for the changes: Above CNS toxicity appears verbatim in the Mevacor label. Sponsor has not submitted any data to justify its removal from the ALTOCOR label.

*2. **Under the heading 'Carcinogenesis, Mutagenesis, Impairment of Fertility'***

In a 21-month carcinogenic study in mice with lovastatin immediate-release there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas 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 lovastatin immediate-release 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 immediate-release].

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 given lovastatin immediate-release. 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 lovastatin immediate-release (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 of lovastatin immediate-release. 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 with lovastatin immediate-release in a microbial mutagen 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.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day with lovastatin immediate-release. 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.

4. Under the heading

4. **Under the heading 'Pregnancy'**

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Lovastatin immediate-release 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/m^2 surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either 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 of lovastatin immediate-release).

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 immediate-release 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 ALTOCOR™ during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. ALTOCOR™ 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 hazard.

Indra Antonipillai, Ph.D.
Pharmacologist, HFD-510

cc: NDA Arch
HFD510
HFD510/antonipillai/davisbruno/pariser/simoneau
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Indra Antonipillai
1/18/02 07:39:10 AM
PHARMACOLOGIST
The labeling changes have been communicated to the sponsor as 'proposed labeld draft 3'
The labeling comments have already been communicated to the sponsor in a proposed labeld draft 3

Karen Davis-Bruno
1/18/02 09:14:21 AM
PHARMACOLOGIST
please enclose a copy of this to the action package