

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-316**

**ADMINISTRATIVE DOCUMENTS**

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-316</u> / SE <u>      </u> - <u>      </u>	
Drug <u>Altacor (lovastatin) Extended Release</u> Tablets; 10, 20, 40, 60 mg	Applicant <u>Aura Laboratories, Inc.</u>
RPM <u>William C. Koch</u>	Phone <u>(301) 827-6412</u>
<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Reference listed drug <u>Mevacor (lovastatin) Tablets [NDA 19-643]</u>	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review	Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P
Pivotal IND(s) <u>      </u>	
Application classifications: Chem Class <u>3</u> Other (e.g., orphan, OTC) <u>      </u>	PDUFA Goal Dates: RS2 Primary <u>July 2, 2002</u> Secondary <u>      </u>

Arrange package in the following order:

Indicate N/A (not applicable),  
X (completed), or add a  
comment.

**GENERAL INFORMATION:**

- ◆ User Fee Information: N/A User Fee Paid  
 User Fee Waiver (attach waiver notification letter)  
 User Fee Exemption
  
- ◆ Action Letter..... XAP  AE  NA
  
- ◆ Labeling & Labels
 

FDA revised labeling and reviews.....	N/A
Original proposed labeling (package insert, patient package insert) .....	X
Other labeling in class (most recent 3) or class labeling.....	X
Has DDMAC reviewed the labeling? .....	<input type="checkbox"/> Yes (include review) <input type="checkbox"/> No
Immediate container and carton labels .....	X
Nomenclature review .....	X
  
- ◆ Application Integrity Policy (AIP) . This application is **not** on the AIP.  
 Exception for review (Center Director's memo)..... \_\_\_\_\_  
 OC Clearance for approval..... \_\_\_\_\_



- ◆ Safety Update review(s) ..... N/A
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver)  Deferred  
Pediatric Page..... X
  - Pediatric Exclusivity requested?  Denied  Granted  Not Applicable
- ◆ Statistical review(s) and memoranda ..... N/A
- ◆ Biopharmaceutical review(s) and memoranda..... X
- ◆ Abuse Liability review(s) ..... N/A  
Recommendation for scheduling .....
- ◆ Microbiology (efficacy) review(s) and memoranda ..... N/A
- ◆ DSI Audits ..... N/A  
 Clinical studies  bioequivalence studies .....

**CMC INFORMATION:**

**Indicate N/A (not applicable),  
X (completed), or add a  
comment.**

- ◆ CMC review(s) and memoranda ..... X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- ◆ DMF review(s) ..... N/A
- ◆ Environmental Assessment review/FONSI/Categorical exemption ..... N/A
- ◆ Micro (validation of sterilization) review(s) and memoranda ..... N/A
- ◆ Facilities Inspection (include EES report)  
Date completed \_\_\_\_\_  Acceptable  Not Acceptable
- ◆ Methods Validation .....  Completed  Not Completed

**PRECLINICAL PHARM/TOX INFORMATION:**

**Indicate N/A (not applicable),  
X (completed), or add a  
comment.**

- ◆ Pharm/Tox review(s) and memoranda ..... N/A
- ◆ Memo from DSI regarding GLP inspection (if any) ..... N/A

- ◆ Statistical review(s) of carcinogenicity studies ..... N/A
- ◆ CAC/ECAC report ..... N/A

**APPEARS THIS WAY  
ON ORIGINAL**



◆ Status of advertising (if AP action) <input type="checkbox"/> Reviewed (for Subpart H – attach review)	<input type="checkbox"/> Materials requested in AP letter
◆ Post-marketing Commitments	_____
Agency request for Phase 4 Commitments.....	_____
Copy of Applicant's commitments .....	_____
◆ Was Press Office notified of action (for approval action only)?.....	<input type="checkbox"/> Yes <input type="checkbox"/> No
Copy of Press Release or Talk Paper.....	_____
◆ Patent	
Information [505(b)(1)] .....	_____
Patent Certification [505(b)(2)].....	<u>N/A</u>
Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....	_____
◆ Exclusivity Summary .....	<u>N/A</u>
◆ Debarment Statement .....	<u>N/A</u>
◆ Financial Disclosure	
No disclosable information .....	<u>N/A</u>
Disclosable information – indicate where review is located .....	_____
◆ Correspondence/Memoranda/Faxes .....	<u>X</u>
◆ Minutes of Meetings .....	<u>N/A</u>
Date of EOP2 Meeting <u>12/09/98</u>	
Date of pre NDA Meeting <u>N/A</u>	
Date of pre-AP Safety Conference <u>N/A</u>	
◆ Advisory Committee Meeting .....	<u>N/A</u>
Date of Meeting .....	_____
Questions considered by the committee .....	_____
Minutes or 48-hour alert or pertinent section of transcript .....	_____
◆ Federal Register Notices, DESI documents .....	<u>N/A</u>

**CLINICAL INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) .....	_____
◆ Clinical review(s) and memoranda .....	<u>"Review" of labeling</u> ← <u>N/A</u>





- ◆ Statistical review(s) of carcinogenicity studies ..... N/A
- ◆ CAC/ECAC report ..... N/A

**APPEARS THIS WAY  
ON ORIGINAL**

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA <u>21-316</u> / SE _____ - _____	
Drug <u>Altacor (lovastatin) Extended Release</u> Applicant <u>Aura Laboratories, Inc.</u> Tablets; 10, 20, 40, 60 mg	
RPM <u>William C. Koch</u> Phone <u>(301) 827-6412</u>	
<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Reference listed drug <u>Mevacor (lovastatin) Tablets [NDA 19-643]</u>	
<input type="checkbox"/> Fast Track	<input type="checkbox"/> Rolling Review
Review priority: <input checked="" type="checkbox"/> S <input type="checkbox"/> P	
Pivotal IND(s) _____	
Application classifications: Chem Class <u>3</u> Other (e.g., orphan, OTC) _____	PDUFA Goal Dates: Primary <u>January 30, 2002</u> Secondary <u>March 30, 2002</u>

Arrange package in the following order:

Indicate N/A (not applicable),  
X (completed), or add a  
comment.

**GENERAL INFORMATION:**

- ◆ User Fee Information:  User Fee Paid  
 User Fee Waiver (attach waiver notification letter)  
 User Fee Exemption
  
- ◆ Action Letter.....  AP  AE  NA
  
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FDA revised labeling and reviews.....	<u>X</u>
Original proposed labeling (package insert, patient package insert) .....	<u>X</u>
Other labeling in class (most recent 3) or class labeling.....	<u>X</u>
Has DDMAC reviewed the labeling? .....	<input type="checkbox"/> Yes (include review) <input type="checkbox"/> No
Immediate container and carton labels .....	<u>X</u>
Nomenclature review .....	<u>X</u>
  
- ◆ Application Integrity Policy (AIP) . This application is **not** on the AIP.
  
- Exception for review (Center Director's memo)..... \_\_\_\_\_
- OC Clearance for approval..... \_\_\_\_\_

- ◆ Status of advertising (if AP action)  Reviewed (for Subpart H – attach review)  Materials requested in AP letter
  
- ◆ Post-marketing Commitments
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant’s commitments .....
  
- ◆ Was Press Office notified of action (for approval action only)?.....  Yes  No
  - Copy of Press Release or Talk Paper.....
  
- ◆ Patent
  - Information [505(b)(1)] .....
  - Patent Certification [505(b)(2)]..... **X**
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
  
- ◆ Exclusivity Summary .....
  
- ◆ Debarment Statement .....
  
- ◆ Financial Disclosure
  - No disclosable information .....
  - Disclosable information – indicate where review is located .....
  
- ◆ Correspondence/Memoranda/Faxes .....
  
- ◆ Minutes of Meetings .....

  - Date of EOP2 Meeting 12/09/98
  - Date of pre NDA Meeting N/A
  - Date of pre-AP Safety Conference N/A

  
- ◆ Advisory Committee Meeting .....

  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....

  
- ◆ Federal Register Notices, DESI documents .....

**CLINICAL INFORMATION:**

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- ◆ Summary memoranda (e.g., Office Director’s memo, Division Director’s memo, Group Leader’s memo) .....
  
- ◆ Clinical review(s) and memoranda .....

- ◆ Safety Update review(s) ..... \_\_\_\_\_
- ◆ Pediatric Information
  - Waiver/partial waiver (Indicate location of rationale for waiver)  Deferred Pediatric Page.....           X
  - Pediatric Exclusivity requested?  Denied  Granted  Not Applicable
- ◆ Statistical review(s) and memoranda .....           X
- ◆ Biopharmaceutical review(s) and memoranda.....           X
- ◆ Abuse Liability review(s) .....           N/A          
  - Recommendation for scheduling ..... \_\_\_\_\_
- ◆ Microbiology (efficacy) review(s) and memoranda .....           N/A
- ◆ DSI Audits .....           N/A          
  - Clinical studies  bioequivalence studies ..... \_\_\_\_\_

**CMC INFORMATION:**

**Indicate N/A (not applicable), X (completed), or add a comment.**

- ◆ CMC review(s) and memoranda .....           X
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability .....           N/A
- ◆ DMF review(s) .....           N/A
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- ◆ Memo from DSI regarding GLP inspection (if any) .....           N/A

- ◆ Statistical review(s) of carcinogenicity studies ..... N/A
- ◆ CAC/ECAC report ..... N/A

**APPEARS THIS WAY  
ON ORIGINAL**

\$  
pd 309,647  
3/22/01

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Form Approved OMB No. 0910-0297 Expiration Date: 04-30-01	
<b>USER FEE COVER SHEET</b>			
<i>See Instructions on Reverse Side Before Completing This Form</i>			
1. APPLICANT'S NAME AND ADDRESS  AURA Laboratories, Inc. Div. of Andrx Corporation 401 Hackensack Avenue Hackensack, N.J. 07601		3. PRODUCT NAME  Lovastatin Extended Release Tablets	
2. TELEPHONE NUMBER (Include Area Code)  (201) 883-1883		4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.  IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW. <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).	
5. USER FEE I.D. NUMBER  4028		6. LICENSE NUMBER / NDA NUMBER  21316	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.			
<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)			
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)			
<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)			
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)			
FOR BIOLOGICAL PRODUCTS ONLY			
<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION			
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY			
<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT			
<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT			
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO (See reverse side if answered YES)			
<b>A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.</b>			
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:			
DHHS, Reports Clearance Officer Paperwork Reduction Project (0910-0297) Hubert H. Humphrey Building, Room 531-H 200 Independence Avenue, S.W. Washington, DC 20201		An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.	
Please DO NOT RETURN this form to this address.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  		TITLE  V.P. Regulatory Affairs	DATE  2/14/01

FORM FDA 3397 (5/98)

Control by Electronic Data Interchange System, USFDA/MS (0910) 0297-01

22 MAR 01  
AURA LABS  
\$ 309,147

### USER FEE VALIDATION SHEET

NDA # 21-316 Supp. Type & # 3S UFID # 4628  
(e.g., N000, SLR001, SE1001, etc.)

1.  YES  NO User Fee Cover Sheet Validated? MIS\_Elements Screen Change(s):  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

2.  YES  NO APPLICATION CONTAINS CLINICAL DATA?  
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.

3. YES  NO SMALL BUSINESS EXEMPTION

4. YES  NO WAIVER GRANTED

5. YES  NO NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other than bundling).  
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division	Fee	No Fee
N _____	HFD- _____	Fee	No Fee
N _____	HFD- _____	Fee	No Fee

6.  YES  NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required  
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N _____	HFD- _____	N _____	HFD- _____

7. P S PRIORITY or STANDARD APPLICATION? *As Filing*

*IS/*

*IS/*

PM Signature / Date

CPMS Concurrence Signature / Date

2/14/00





Lovastatin  
141-118



US005916595A

United States Patent [19]

[11] Patent Number: 5,916,595

Chen et al.

[45] Date of Patent: Jun. 29, 1999

[54] HMG CO-REDUCTASE INHIBITOR

5,518,730 5/1996 Fuisz ..... 424/426

[75] Inventors: Chih-Ming Chen, David; Joseph Chou, Coral Springs; David Wong, Hollywood, all of Fla.

5,543,154 8/1996 Rock et al. .... 424/473  
5,582,838 12/1996 Rock et al. .... 424/472  
5,616,593 4/1997 Patel et al. .... 514/521

OTHER PUBLICATIONS

[73] Assignee: Andrx Pharmaceuticals, Inc., Fort Lauderdale, Fla.

Hatano, Harumi et al., Pharmaceutical Preparation inform of Coated Capsule Releasable at Lower Part of Digestive Tract, Capius, 1997:195672.

[21] Appl. No.: 08/989,253

Primary Examiner—Jose' G. Dees  
Assistant Examiner—Michael A. Williamson  
Attorney, Agent, or Firm—Hedman, Gibson & Costigan, P.C.

[22] Filed: Dec. 12, 1997

[51] Int. Cl.<sup>6</sup> ..... A61K 9/36

[52] U.S. Cl. .... 424/480; 514/529

[58] Field of Search ..... 514/529; 424/480

[57] ABSTRACT

A controlled release dosage formulation is described which is based on a combination of:

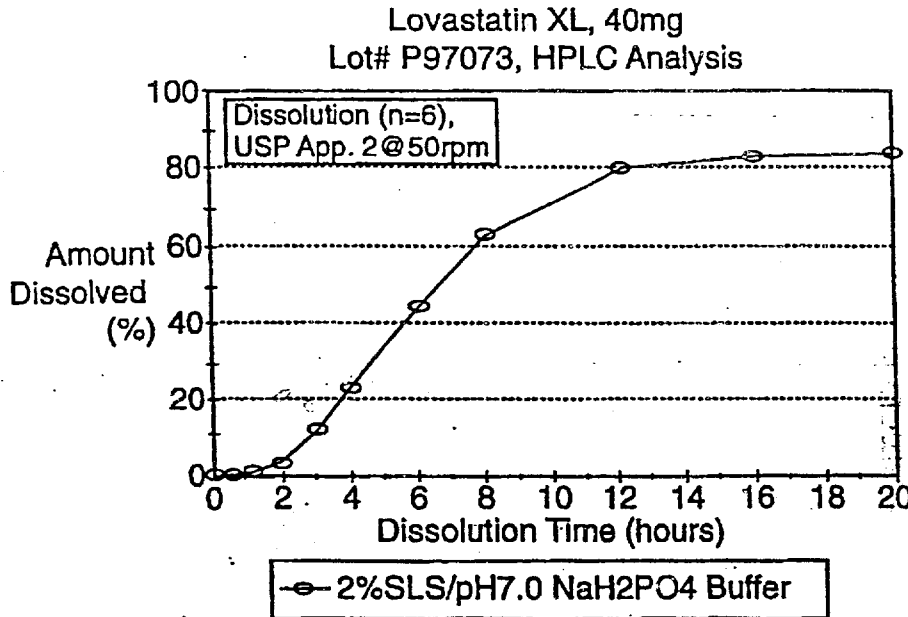
- (a) a compressed tablet core which contains an alkyl ester of a hydroxy substituted naphthalene derivative a pharmaceutically acceptable, water swellable polymer and an osmotic agent; and
- (b) an outer coating layer which completely covers the osmotic core and comprises a pH sensitive coating agent and a water insoluble polymer.

[56] References Cited

U.S. PATENT DOCUMENTS

4,814,183	3/1989	Zentner .....	424/485
4,915,954	4/1990	Ayer et al. ....	424/473
4,946,686	8/1990	McClelland et al. ....	424/473
4,976,967	12/1990	McClelland et al. ....	424/473
5,244,916	9/1993	Bokoch .....	514/460
5,300,288	4/1994	Albright .....	424/78.08
5,350,584	9/1994	McClelland et al. ....	424/501
5,366,738	11/1994	Rock et al. ....	424/473

12 Claims, 3 Drawing Sheets



Lovastatin XL, 40mg  
Lot# P97073, HPLC Analysis

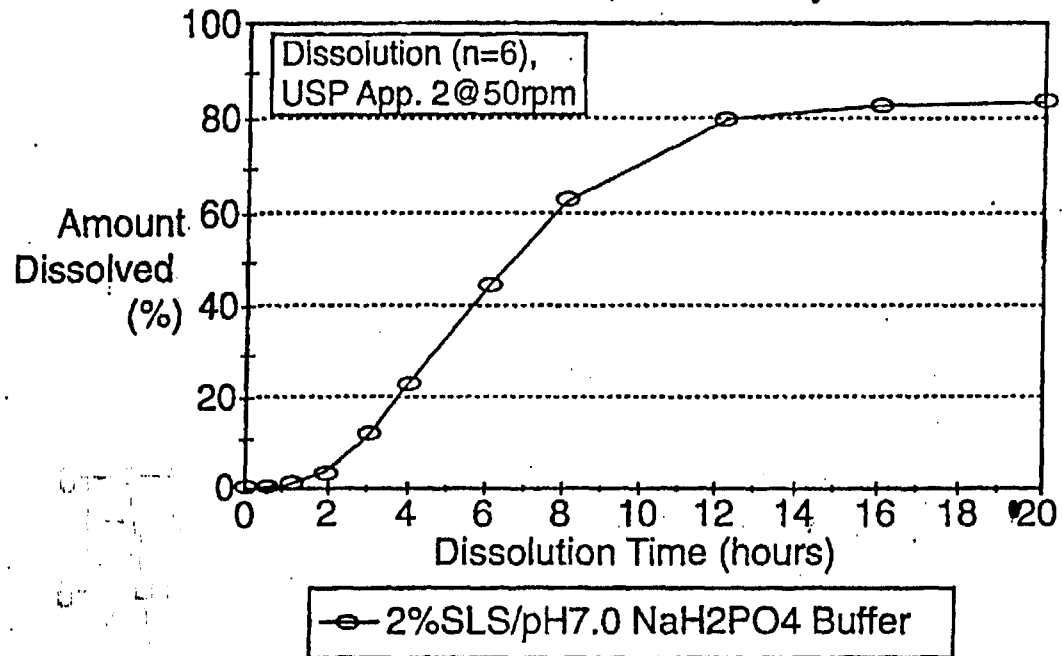


FIG. 1

Final  
Conc.  
(mg/mL)

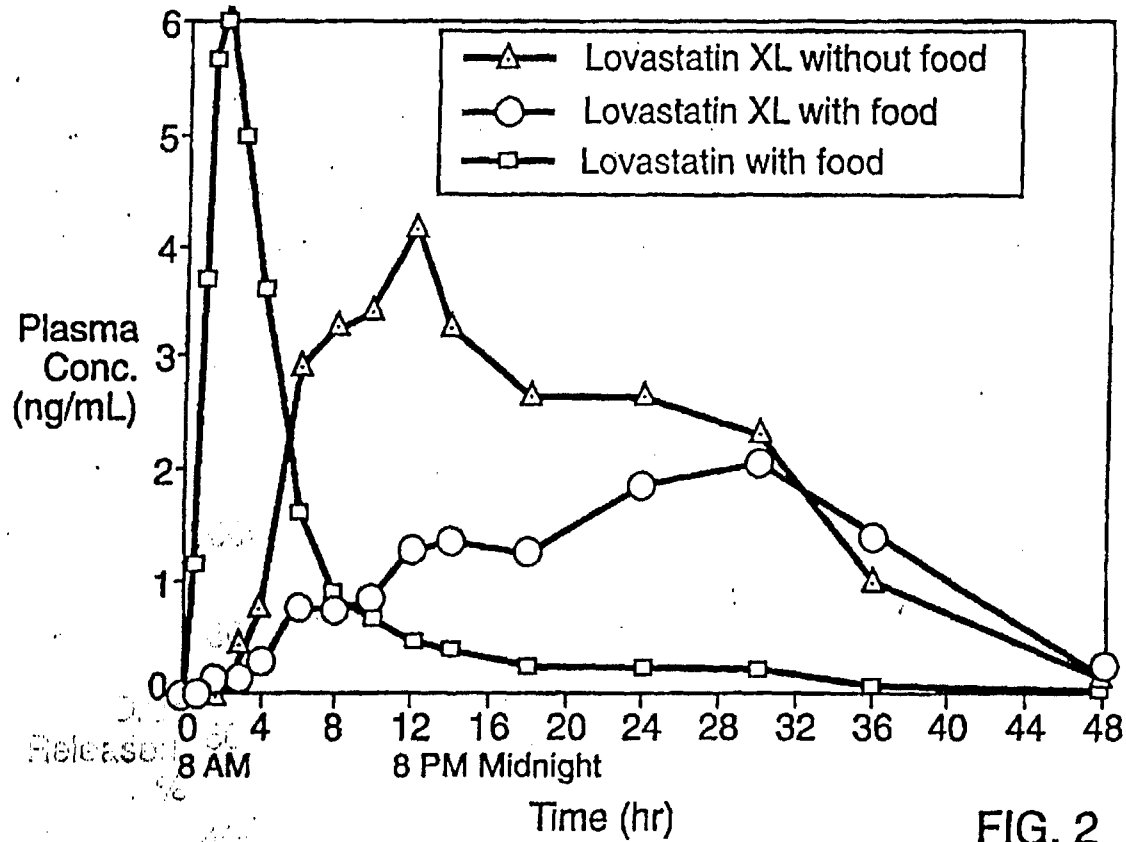


FIG. 2

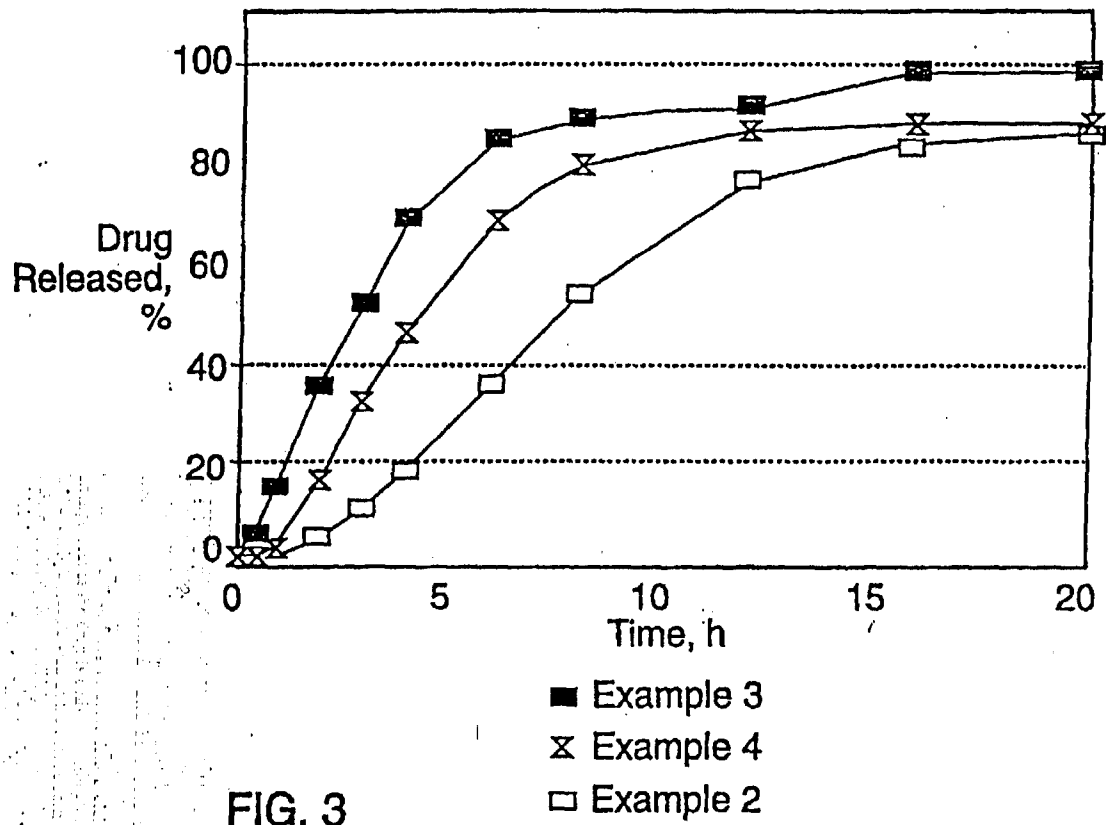


FIG. 3

## HMG CO-REDUCTASE INHIBITOR BACKGROUND OF THE INVENTION

The use of HMG-CoA reductase inhibitors for the reduction of serum cholesterol levels is well known. These compounds include alkyl esters of hydroxy substituted naphthalenes which are orally effective in the reduction of serum cholesterol levels. Examples of these compounds include mevastatin which is described in U.S. Pat. No. 3,671,523; lovastatin which is described in U.S. Pat. No. 4,231,938; pravastatin which is described in U.S. Pat. No. 4,346,227; and simvastatin which is described in U.S. Pat. No. 4,444,784. All of these patents are incorporated by reference.

Lovastatin is a metabolite which is produced by the natural fermentation of a fungus of the *Aspergillus* genus. Lovastatin acts systemically to lower blood serum cholesterol levels by disrupting the biosynthesis of cholesterol in the liver, where 70% to 80% of body cholesterol is produced. Specifically lovastatin interrupts a step in the endogenous production of cholesterol by inhibiting the HMG coenzyme A reductase from combining with bile acids in the digestive tract such that the bile acids are excreted from the body without reabsorption. With synthesis in the liver thus inhibited, the liver cells must take cholesterol from the bloodstream, and they do so by increasing their production of cell surface receptors for LDL cholesterol. Lovastatin formulations are generally capable of lowering the blood serum cholesterol level by about 30-40%. The other compounds of this class are derived from natural or synthetic sources using well known procedures and have similar mechanisms of activity.

However, it is desirable to enhance the activity of these compounds to achieve even greater reductions of blood serum cholesterol levels in connection with the treatment of hypercholesterolemia and other maladies. Accordingly, the present invention provides a novel controlled release formulation of a compound which is an alkyl ester of a hydroxy substituted naphthalene derivative which provides for a gradual release of the compound. This formulation has been prepared to provide a slow controlled release of these compounds in order to provide a more constant level of bioavailability in order to provide an enhanced effect that cannot be achieved by conventional immediate release dosing. The use of a controlled release form of is believed to be specially useful for those who have meals at irregular times or those who frequently eat snacks between meals. These subjects include night shift workers, airline personnel and travelers, and those individuals with blood sugar problems who eat frequent small meals. In addition, it is believed that the human body synthesizes high amounts of cholesterol during the hours of sleep and it is desirable in certain cases to provide therapeutic level of these compounds during periods of sleep.

Controlled release formulations have been described in U.S. Pat. No. 4,615,698 which have been based on an osmotic dosage form which is designed to collapse and cause the faced surfaces to come into a close contacting arrangement as the drug is delivered through a passageway in the semi-permeable wall of the dosage form. In addition, U.S. Pat. No. 4,503,030 discloses an osmotic dosage form which has a passageway and a semi-permeable membrane consisting of a particular cellulose polymer and a pH sensitive material which could be an enteric coating material. This patent describes the use of 1:1 mixtures of a pH sensitive material and cellulose polymer which are applied at a level of about 7% by weight based on the total weight of the osmotic core tablet and coating material.

The applicants have discovered that a ratio of 0.75:1, and lower, of pH sensitive material to cellulose polymer may be used to provide a stable membrane around an osmotic core tablet at a coating level of 1-4% by weight based on the total weight of the osmotic core tablet and coating material. These osmotic tablets will substantially, completely deliver the compound without the need to provide a passageway in the tablet according to the teachings of the prior art. In addition the osmotic tablet of the invention will provide higher bioavailability and lower peak plasma drug concentrations than are provided by the same weight of the alkyl ester of a hydroxy substituted naphthalene derivative in a conventional immediate release dosage form.

## SUMMARY OF THE INVENTION

The present invention provides a controlled release lovastatin dosage formulation which comprises:

- (a) a compressed tablet core which contains an alkyl ester of a hydroxy substituted naphthalene derivative, a pharmaceutically acceptable, water swellable polymer and an osmotic agent; and
- (b) an outer coating layer which completely covers the osmotic core and comprises a pH sensitive coating agent and a water insoluble polymer.

An optional sealing coat may be applied to the compressed tablet core and an optional coating layer comprising an enteric coating agent may be applied under the outer coating layer as an inner coating or as an overcoat over the outer coating layer. The tablet core may be compressed using a smooth faced tablet die. The preferred alkyl ester of a hydroxy substituted naphthalene compound is lovastatin.

Accordingly, it is a primary object of the present invention to provide a controlled release form of an alkyl ester of a hydroxy substituted naphthalene derivative.

It is also an object of the present invention to provide a controlled release dosage formulation of an alkyl ester of a hydroxy substituted naphthalene derivative which substantially completely releases said alkyl ester in about 4 to 30 hours in vitro in a Type 2 USP 23 dissolution apparatus in 2% sodium lauryl sulfate, pH buffer to 7.0 at 37° C. and 50 rpm.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph of in vitro dissolution data which shows the dissolution profile of the formulation of Example 1 in 2% sodium lauryl sulfate at pH 7.0 in NaH<sub>2</sub>PO<sub>4</sub> buffer in a USP XXII Type II dissolution apparatus at 50 rpm at 37° C.

FIG. 2 is a graph of comparative data which shows the in vivo effect of a conventional immediate release dose of 40 mg of lovastatin and the in vivo effect of an extended release dose, according to the invention, of 40 mg of lovastatin.

FIG. 3 is a graph of in vitro dissolution data which shows the dissolution profiles of the formulations of Examples 2, 3 and 4 in 2% sodium lauryl sulfate at pH 7.0 in NaH<sub>2</sub>PO<sub>4</sub> buffer in a USP XXII Type II dissolution apparatus at 50 rpm at 37° C.

## DETAILED DESCRIPTION OF THE INVENTION

The controlled release dosage form is preferably prepared by combining mevastatin, pravastatin, simvastatin or lovastatin with a pharmaceutically acceptable, water swellable polymer and an osmotic agent into a compressed tablet core having an optional first coating for sealing and protection and a second coating comprising a pH sensitive agent water

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insoluble polymer. Mevastatin, pravastatin, simvastatin and lovastatin are well known compounds that are described in the prior art including the particular patents which have been cited herein. It is also within the scope of the invention to use mixtures of different alkyl esters of hydroxy substituted naphthalenes.

Specifically, a pharmaceutically acceptable, water swellable polymer and an osmotic agent are combined with the drug which may be micronized or unmicronized or amorphous or crystalline and compressed to form the tablet core. The osmotic agent is any non-toxic pharmaceutically acceptable water soluble compound which will dissolve sufficiently in water and increase the osmotic pressure inside the core of the tablet. The osmotic agents include the simple sugars and salts such as sodium chloride, potassium chloride, magnesium sulfate, magnesium sulfate, magnesium chloride, sodium sulfate, lithium sulfate, urea, inositol, sucrose, lactose, glucose, sorbitol, fructose, mannitol, dextrose, magnesium succinate, potassium acid phosphate and the like. The preferred osmotic agent for the tablet core is a simple sugar such as anhydrous lactose in the range of 0-50% by weight, based on the weight of the compressed, uncoated tablet.

The pharmaceutically acceptable, water swellable polymer may be any pharmaceutically acceptable polymer which swells and expands in the presence of water to slowly release the lovastatin. These polymers include polyethylene oxide, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose and the like. In a preferred embodiment, the water swellable polymer will be polyethylene oxide (obtained from Union Carbide Corporation under the trade name Polyox WSR Coagulant or Polyox WSR N 80). These materials form a viscous gel in water or other solvent system at a sufficient concentration to control the release of the lovastatin. This will generally require a concentration of the pharmaceutically acceptable, water swellable polymer of about 0-50% by weight of the compressed, uncoated tablet.

Binder may be employed in a sufficient amount so that when it is combined with a suitable solvent, mixed with the water soluble osmotic agent and agitated, granules will be formed which may be compressed into a tablet core. Prior to compressing the granules, the conventional solid pharmaceutical diluents such as microcrystalline cellulose, lactose, dextrose and the like may be added to the granule forming mixture in amounts from about 0 to 51% weight based on the weight of the compressed, uncoated tablet. In the present case, the above mentioned osmotic agent, lactose, may function as a binder in the tablet compression step.

In the preparation of the tablets of the invention, various solvents may be used to prepare the granules. In addition, various other diluents, excipients, lubricants, dyes, pigments, dispersants, emulsifiers, etc. may be used to optimize the formulations of the invention.

Additionally, a surfactant is used in the preferred embodiment. The surfactant may be any ionic or non-ionic water soluble surfactant which may be employed in the range of 0-50% by weight or preferably 1-5% by weight. The preferred surfactant for the present formulation is sodium lauryl sulfate but other surfactants such as polysorbate 20, 60 or 80; polyoxi 40 stearate and the like.

Furthermore, the preferred embodiment may comprise a lubricant. Ideally, the lubricant will be in the range of 0.5 to 2.5% by weight of the compressed, uncoated tablet.

After the above described tablet core is formed, it is coated with: 1) an optional protective first coating on the tablet core and/or an optional pH sensitive coating; 2) an

outer coating comprising a pH sensitive agent and a water insoluble polymer.

Specifically, a protective first coating may be used at a level in the range of 0-10% by weight which may be applied from a coating system such as Opadry Clear sold by Colorcon Corporation. In an especially preferred embodiment, the Opadry Clear will be 2.83% by weight and will be combined with an osmotic agent in the range of 0-10% by weight. While the osmotic agent may be any salt, low molecular weight molecule or water soluble polymers, the preferred agent is sodium chloride. The osmotic agent is added to the coating system when the coating system is being dispersed into purified water. The coating system which contains the osmotic agent may then be sprayed onto the tablets to form a protective coating layer. As mentioned above, this protective first coating is optional.

An optional inner or over coat over the outer coat may also be applied which comprises a pH sensitive polymer which functions as an enteric polymer in that it does not begin to dissolve until pH conditions in excess of the stomach region are encountered. Generally, the pH sensitive materials do not dissolve and begin to release the active drug until a pH above 3.0 and preferably above 5.5. Materials such as such as Eudragit L (copolymer of poly(methacrylic acid, methylmethacrylate), 1:1 ratio; MW (No. Av. 135,000 - USP Type A) or Eudragit S (copolymer of poly(methacrylic acid, methylmethacrylate), 1:2 ratio MW (No. Av. 135,000 - USP Type B), hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate and the like may be used in the range of 0-3% by weight and preferably, 2 to 4 percent by weight of the combined weight of the compressed, uncoated tablet and the inner coating of the pH sensitive polymer.

The outer coating comprises a pH sensitive polymer which functions as an enteric polymer in that it does not begin to dissolve until pH conditions in excess of the pH of the stomach region are encountered and a water insoluble polymer which provide controlled release properties to the coating formulation. The pH sensitive polymer is the same type of material that is described above as the optional inner coating layer. The water insoluble polymer may be a cellulosic polymer such as ethylcellulose, cellulose acrylate, cellulose mono-, di- or triacetate. The pH sensitive polymer and the insoluble cellulosic polymer are used at a weight ratio of about 0.1: to 0.75:1 preferably 0.25:1 to 0.5:1 of pH sensitive polymer to water insoluble cellulosic polymer. A combined coating weight of about 0.5-5% by weight and preferably 1 to 4% by weight and especially preferred is 1 to 3% by weight of the gained weight based on the weight of the coated tablet core. Cellulose acetate is the preferred water insoluble polymer and the outer coating is preferably applied as a suspension in acetone.

Furthermore, a plasticizer or combination of plasticizers may be added to the inner, outer or over coating to provide elasticity and shape to the coating. While the plasticizer or combination of plasticizers may be any water soluble or water insoluble formulation in the range of 0-10% by weight and preferably 0.5 to 5% by weight of the outer coating composition. Acetyltributyl citrate is the preferred plasticizer but materials such as acetyl triethyl citrate, dibutyl phthalate, triacetin, diethyl phthalate, polyethylene glycol, propylene glycol and the like may be utilized.

An antioxidant such as BHA or BHT may be added to the tablet core as a stabilizer at a level of 0.001 to 0.01 by weight of the tablet core.

Lastly, a channelling agent is mixed with the aforementioned components of the outer coating. A channelling agent

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may be employed to increase the porosity of the film coating in order to increase the amount of the fluids that penetrate the tablet core and increase the rate of hydration. This allows the release of the lovastatin after the outer film coat ruptures. Generally, channelling agents may be any salts, surfactants, or short-chain water soluble polymers in a water channel forming effective amount i.e. 1 to 5% by weight, based on the total weight of the core and all coating components. The channelling agents include any pharmaceutically acceptable water soluble salt, surfactant, or short chain water soluble polymer such as sodium chloride, potassium chloride, sucrose, polysorbate-80, hydroxypropyl cellulose, hydroxyethyl cellulose and the like.

Also, the preferred embodiment of the inner or over coating is supplied with an anti-sticking agent such as talc to overcome any tablet to tablet stickiness during the coating process. The amount of anti-sticking agent is an amount which prevents sticking which may be in the range of 0-6% by weight based on the weight of the tablets and the coating materials on a dry weight basis.

Although the applicants do not wish to be bound by any theory by which the invention operates, it is believed that the tablets of the invention release the lovastatin by osmotic pressure. Water is drawn into the tablet and it expands to the point where the outer coating fails in one particular area to form a constricted opening which releases the internal contents of the tablet which contain the drug. Thereafter, the aqueous medium of the tablet shell will continue to release the drug as it dissolves until the osmotic pressure inside the tablet shell equals that of the surrounding environment. At the late stages of the in vivo release of lovastatin, it is believed that the tablet shell will collapse and/or disintegrate completely to substantially completely release the remaining drug. The water insoluble coating is not absorbed in the gastrointestinal tract and is eliminated in the feces.

The tablets of the invention may be made in a smooth faced tablet die. Thereafter the tablet is provided with the outer coating which, because of surface tension, will result in a thinner coating layer over the corners of the tablet which will provide an area in the outer coating which will form a channel to allow intestinal fluid to reach the core of the tablet.

The tablets of the invention will have the following general formula:

INGREDIENTS	POSSIBLE RANGE, wt %
<u>Tablet Core</u>	
Alkyl ester of a substituted asphaltene	3-20
Water Swellable Polymer	10-40
Antioxidant	0.001-0.01
Osmotic Agents	20-80
Surfactant	0-5
Lubricant	0-5
<u>Coatings:</u>	
Seal Coating	0-10
Osmotic Agents	0-30
<u>Inner Coating</u>	
Enteric Polymer	0-30
Anti-sticking Agent	0-6
Plasticizer	0-6
Channelling Agents	0-6

-continued

INGREDIENTS	POSSIBLE RANGE, wt %
<u>Outer Coating</u>	
Bleed of Enteric Polymer and Water-insoluble Polymer	0.5-5
Plasticizer(s)	0-1
Channelling Agents	0.2-5
<u>Overcoat</u>	
Enteric Polymer	0-30
Anti-sticking Agent	0-6
Plasticizer	0-6
Channelling Agents	0-6
TOTAL	100

DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

A tablet having the following formula was prepared:

lovastatin	11.99 wt %	40.0 mg
Polyox WSR Coagulant, NF*	4.50 wt %	15.0 mg
Polyox WSR N 80, NF**	17.98 wt %	60.0 mg
lactose (anhydrous)	50.65 wt %	169.0 mg
sodium lauryl sulfate	3.00 wt %	10.0 mg
silicon dioxide Fumed USP/NF	0.45 wt %	1.5 mg
Myvaplex 600P***	1.80 wt %	6.0 mg
<u>Seal Coating:</u>		
Opadry Clear****	2.81 wt %	9.4 mg
sodium chloride	0.93 wt %	3.1 mg
<u>Inner Coating:</u>		
hydroxypropylmethylcell. phthal.55	2.27 wt %	7.58 mg
talc	0.78 wt %	2.6 mg
acetyl tributyl citrate	0.22 wt %	0.75 mg
sugar, confectioners 6X micronized	0.62 wt %	2.08 mg
<u>Outer Coating:</u>		
cellulose acetate	1.00 wt %	3.32 mg
Endrag S 100†	0.34 wt %	1.13 mg
tricresin	0.08 wt %	0.27 mg
polyethylene glycol 400	0.08 wt %	0.27 mg
sugar, confectioners 6X micronized	0.50 wt %	1.66 mg
	100.0 wt %	333.66 mg

\*polyethylene oxide Mw No av 5,000,000  
 \*\*polyethylene oxide Mw No av 200,000  
 \*\*\*glyceryl monostearate  
 \*\*\*\*lacquer containing hydroxypropyl methyl cellulose and polyethylene glycol  
 †Endrag S 200 (poly(methacrylic acid, methylmethacrylate, 1:2 ratio MW (No. Av. 135,000) - USP Type B)

The following describes the process of making the above described dosage form:

STEP 1, THE TABLET CORE

(a) Granulation

1. Pass Polyox WSR N80, sodium lauryl sulfate and anhydrous lactose through a 30 mesh stainless steel screen.
2. Charge the screened materials and lovastatin (micronized) into a vertical granulator.
3. Dissolve butylated hydroxy anisole in ethanol.
4. Mix ethanol, and purified water.
5. Pre-mix the powder mixture for 5 minutes.
6. Blend the powder mixture again, add the butylated hydroxyanisole solution and then the ethanol/water mixture.
7. Dry the granules at 45-50° C. until the moisture content is lower than 1.8 wt %.
8. Pass the granules through a 1575 mesh using a Comil.

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Tabletting

1. Mix Cab-O-Sil and Polyox WSR N80.
2. Pass the mixture of Cab-O-Sil and Polyox WSR N80 through a 24 mesh stainless steel screen with the Polyox WSR Coagulant.
3. Blend the screen materials with lovastatin granules for 15 minutes.
4. Pass Myvaplex through a 30 mesh stainless steel screen and combine with the other screen materials.
5. Blend for five minutes.
6. Compress the blend into tablets (300 mg. round, standard concave, 1/2") which contain 40 mg of lovastatin.

Seal Coating: Opadry Clear

1. Dissolve sodium chloride in purified water.
2. Disperse Opadry Clear into the sodium chloride solution.

3. Spray lovastatin tablets with the aqueous coating suspension using a coater.

Inner Coating: Hydroxypropyl methylcellulose phthalate 55

1. Dissolve hydroxypropyl methylcellulose phthalate 55 in acetone using a homogenizer.
2. Add acetyl tributyl citrate to the acetone solution and mix it with a homogenizer until a homogenized dispersion is obtained.
3. Add talc and sugar to the solution and mix it with a homogenizer until a homogenized dispersion is obtained.

4. Replace the homogenizer with a magnetic mixer and stir the coating mixture throughout the coating process.

5. Spray the Opadry Clear coated lovastatin tablets with the coating dispersion in a coater.

Outer Coating: cellulose acetate

1. Dissolve cellulose acetate and Eudragit S100 in acetone using a homogenizer.
2. Add polyethylene glycol 400, triacetin and sugar to the solution and mix until a homogeneous dispersion is obtained.

3. Spray the coating suspension onto the tablets in a coater.

Release in the above described manner will result in the dissolution profile shown in FIG. 1:

It is believed that administration of the above described micronized Lovastatin in these amounts will be particularly effective in inhibiting the biosynthesis of cholesterol in the liver through interruption of HMG coenzyme A reductase. The dosage of lovastatin should be individualized depending on the desired and/or degree of serum cholesterol that is desired. Generally 10 to 80 mg of lovastatin per day should be administered by mouth depending on the response and the degree of reduction in serum cholesterol level that is indicated.

EXAMPLE 2

A tablet having the following formula was prepared:

lovastatin	12.11 wt %	40.0 mg
Polyox WSR Coagulant, NF*	4.54 wt %	15.0 mg
Polyox WSR N 80, NF**	17.71 wt %	58.5 mg
lactose (anhydrous)	51.13 wt %	168.9 mg
sodium lauryl sulfate	3.03 wt %	10.0 mg
silicon dioxide Fumed USP/NF	0.45 wt %	1.5 mg

-continued

butylated hydroxy anisole	0.03 wt %	0.10 mg
Myvaplex 600***	1.82 wt %	6.0 mg
<u>Seal Coating:</u>		
Opadry Clear****	2.85 wt %	9.4 mg
sodium chloride	0.94 wt %	3.1 mg
<u>Inner Coating:</u>		
hydroxypropylmethylcell. phthal 55	2.29 wt %	7.58 mg
talc	0.79 wt %	2.6 mg
acetyl tributyl citrate	0.23 wt %	0.75 mg
sugar, confectioners 6X micronized	0.08 wt %	0.27 mg
<u>Outer Coating:</u>		
cellulose acetate	1.00 wt %	3.32 mg
Eudragit S 100 <sup>†</sup>	0.34 wt %	1.13 mg
triacetin	0.08 wt %	0.27 mg
polyethylene glycol 400	0.08 wt %	0.27 mg
sugar, confectioners 6X micronized	0.50 wt %	1.66 mg
	100.0 wt %	330.35 mg

\*polyethylene oxide Mw No sv 3,000,000  
 \*\*polyethylene oxide Mw No sv 200,000  
 \*\*\*glyceryl monostearate  
 \*\*\*\*mixture containing hydroxypropyl methyl cellulose and polyethylene glycol  
<sup>†</sup>Eudragit S 100 (poly(methacrylic acid, methylmethacrylate, 1:2 ratio MW (No. Av. 135,000 - USP Type B)

Coated tablets were prepared using the general procedure of Example 1.

EXAMPLE 3

A tablet having the following formula was prepared:

lovastatin	12.14 wt %	20.0 mg
Polyox WSR Coagulant, NF*	4.55 wt %	7.5 mg
Polyox WSR N 80, NF**	17.76 wt %	29.25 mg
lactose (anhydrous)	51.30 wt %	84.5 mg
sodium lauryl sulfate	3.04 wt %	5.0 mg
silicon dioxide Fumed USP/NF	0.46 wt %	0.75 mg
butylated hydroxy anisole	0.03 wt %	0.05 mg
Myvaplex 600***	1.82 wt %	3.0 mg
<u>Seal Coating:</u>		
Opadry Clear****	3.42 wt %	5.63 mg
sodium chloride	1.14 wt %	1.88 mg
<u>Outer Coating:</u>		
cellulose acetate	1.43 wt %	2.36 mg
Eudragit S 100 <sup>†</sup>	0.49 wt %	0.80 mg
triacetin	0.11 wt %	0.19 mg
polyethylene glycol 400	0.11 wt %	0.19 mg
sugar, confectioners 6x micronized	0.72 wt %	1.18 mg
<u>Overcoat:</u>		
hydroxypropylmethylcell. phthal 55	0.77 wt %	1.27 mg
talc	0.30 wt %	0.49 mg
triacetin	0.12 wt %	0.20 mg
sugar, confectioners 6x micronized	0.30 wt %	0.49 mg
	100.0 wt %	144.73 mg

\*polyethylene oxide Mw No sv 3,000,000  
 \*\*polyethylene oxide Mw No sv 200,000  
 \*\*\*glyceryl monostearate  
 \*\*\*\*mixture containing hydroxypropyl methyl cellulose and polyethylene glycol  
<sup>†</sup>Eudragit S 100 (poly(methacrylic acid, methylmethacrylate, 1:2 ratio MW (No. Av. 135,000 - USP Type B)

The following describes the process of making the above-described dosage form:

STEP 1, THE TABLET CORE

(a) Granulation

1. Pass Polyox WSR N80, sodium lauryl sulfate and anhydrous lactose through a 30 mesh stainless steel screen.
2. Charge the screened materials and lovastatin (micronized) into a vertical granulator.

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3. Dissolve butylated hydroxy anisole in ethanol.
4. Mix ethanol and purified water.
5. Pre-mix the powder mixture for 5 minutes.
6. Blend the powder mixture again, add the butylated hydroxyanisole solution and then the ethanol/water mixture.
7. Dry the granules at 45-50° C. until the moisture content is lower than 1.8 wt %.
8. Pass the granules through a 1575 mesh using a Comil.

Tabletting

1. Mix Cab-O-Sil and Polyox WSR N80.
2. Pass the mixture of Cab-O-Sil and Polyox WSR N80 through a 24 mesh stainless steel screen with the Polyox WSR Coagulant.

3. Blend the screen materials with lovastatin granules for 15 minutes.

4. Pass Myvaplex through a 30 mesh stainless steel screen and combine with the other screen materials.

5. Blend for five minutes.
6. Compress the blend into tablets (164.72 mg, round, standard concave, 1/4" dia.) which contain 20 mg of lovastatin.

Seal Coating: Opadry Clear

1. Dissolve sodium chloride in purified water.
2. Disperse Opadry Clear into the sodium chloride solution.

3. Spray lovastatin tablets with the aqueous coating suspension using a coater.

Inner Coating: None

Outer Coating: cellulose acetate

1. Dissolve cellulose acetate and Eudragit S100 in acetone using a homogenizer.

2. Add polyethylene glycol 400, triacetin and sugar to the solution and mix until a homogeneous dispersion is obtained.

3. Spray the coating suspension onto the tablets in a coater.

Overcoating: Hydroxypropyl methylcellulose phthalate 55

1. Dissolve hydroxypropyl methylcellulose phthalate 55 in acetone using a homogenizer.

2. Add acetyl tributyl citrate to the acetone solution and mix it with a homogenizer until a homogenized dispersion is obtained.

3. Add talc and sugar to the solution and mix it with a homogenizer until a homogenized dispersion is obtained.

4. Replace the homogenizer with a magnetic mixer and stir the coating mixture throughout the coating process.

5. Spray the Opadry Clear coated lovastatin tablets with the coating dispersion in a coater.

EXAMPLE 4

A tablet having the following formula was prepared:

lovastatin	32.20 wt %	20.0 mg
Polyox WSR Coagulant, NF*	4.57 wt %	7.5 mg
Polyox WSR N 80, NF**	17.84 wt %	29.25 mg
Inucose (anhydrous)	51.53 wt %	84.5 mg
sodium lauryl sulfate	3.05 wt %	5.0 mg
silicon dioxide Pharmed USP/NF	0.46%	0.75 mg
butylated hydroxy anisole	0.03 wt %	0.05 mg
Myvaplex 600P***	1.83 wt %	3.0 mg

-continued

Seal Coating:		
Opadry Clear****	1.43 wt %	5.43 mg
sodium chloride	1.15 wt %	1.88 mg
Inner Coating:		
None		
Outer Coating:		
cellulose acetate	1.96 wt %	3.21 mg
Eudragit S 100†	0.66 wt %	1.09 mg
acetyl tributyl citrate	0.32 wt %	0.52 mg
sugar, confectioners for micronized	0.96 wt %	1.61 mg
	100.00 wt %	163.99 mg

- 15 \*polyethylene oxide Mw No av 5,000,000
- \*\*polyethylene oxide Mw No av 200,000
- \*\*\*glyceryl monostearate
- \*\*\*\*mixture containing hydroxypropyl methyl cellulose and polyethylene glycol

- 20 Coated tablets were prepared using the general procedure of Example 3 except that no inner coating was applied and an outer enteric coating was applied as an overcoat over the outer layer.

- 25 A comparison of Examples 2, 3 and 4 shows that the following was the weight of the coatings that were applied:

Example 2	Inner Coating	4 wt %
	Outer Coating	2 wt %
	Over Coating	0%
Example 3	Inner Coating	0%
	Outer Coating	3 wt %
	Over Coating	2.5%
Example 4	Inner Coating	0 wt %
	Outer Coating	4 wt %
	Over Coating	0 wt %

- 35 It is believed that administration of the above described micronized Lovastatin in these amounts will be particularly effective in inhibiting the biosynthesis of cholesterol in the liver through interruption of HMG coenzyme A reductase.
- 40 The dosage of lovastatin should be individualized depending on the desired and/or degree of serum cholesterol that is desired. Generally 10 to 80 mg of lovastatin per day should be administered by mouth depending on the response and the degree of reduction in serum cholesterol level that is indicated.

- 45 The foregoing description of a preferred embodiment of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention precise form disclosed. Obvious modifications or variations are possible in light of the above teachings. All such obvious modifications and variations are intended to be within the scope of the appended claims.

We claim:

- 35 1. A controlled release formulation containing an alkyl ester of a hydroxy substituted naphthalene compound, said formulation comprising:

- 40 (a) a compressed tablet core which contains an alkyl ester of a hydroxy substituted naphthalene compound, a pharmaceutically acceptable, water swellable polymer and an osmotic agent; and
- 45 (b) an outer coating layer which completely covers the osmotic core and comprises a pH sensitive coating agent, a channelling agent and a water insoluble cellulose polymer used at a weight ratio of 0.1:1 to 0.75:1 and at a combined coating weight of 0.5-5% by weight.

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2. A controlled release formulation as defined in claim 1 wherein the alkyl ester of a hydroxy substituted naphthalene compound is selected from the group consisting of mevastatin, pravastatin, simvastatin and lovastatin.

3. A controlled release dosage form as defined in claim 2 wherein said compressed tablet core is provided with a first coating to seal the tablet core.

4. A controlled release dosage form as defined in claim 2 wherein said compressed tablet core is provided with an inner enteric coating.

5. A controlled release dosage form as defined in claim 2 wherein said compressed tablet core is provided with an overcoat which is an enteric coating.

6. A controlled release dosage form as defined in claim 2 wherein the pharmaceutically acceptable water swellable polymer is polyethylene oxide.

7. A controlled release dosage form as defined in claim 2 wherein the osmotic agent is anhydrous lactose.

8. A controlled release dosage form as defined in claim 2 wherein the pH sensitive coating agent is a copolymer of poly(methacrylic acid and methylmethacrylate.

9. A controlled release dosage form as defined in claim 2 wherein the tablet core contains a surface active agent.

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10. A controlled release dosage form as defined in claim 2 wherein the tablet core contains sodium lauryl sulfate.

11. A controlled release dosage form which comprises:

(a) a compressed tablet core which comprises lovastatin, a polyoxyethylene water swellable polymer and anhydrous lactose;

(b) an outer coating layer which comprises a mixture of a copolymer of poly(methacrylic acid/methylmethacrylate and a cellulose acetate polymer at a weight ratio of 0.1:1 to 0.75:1.

12. A controlled release dosage formulation which comprises:

(a) a compressed tablet core comprising lovastatin, a pharmaceutically acceptable, water swellable polymer and an osmotic agent;

(b) an inner coating layer which comprises a pH sensitive coating agent; and

(c) an outer coating layer which comprises a pH sensitive coating agent, a channeling agent and a water insoluble cellulosic polymer.

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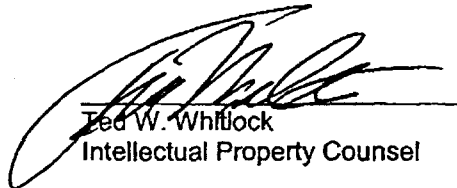
ANDREX COMPANY



Paragraph III Certification

Aura Laboratories, Inc., a subsidiary of Andrx Corporation, according to 21 Code of Federal Regulations Part 314.50 (g)(2)(i) certifies that in our opinion and to the best of our knowledge the patent covering Mevacor® (lovastatin) Tablets, marketed by Merck & Co., Inc., U.S. Patent Number 4,231,938 will expire on June 15, 2001.

Aura Laboratories, Inc. will not market its (lovastatin, USP) Extended-release Tablets prior to the expiration of U.S. Patent Number 4,231,938.



Ted W. Whitlock  
Intellectual Property Counsel

February 27, 2001  
Date

**APPEARS THIS WAY  
ON ORIGINAL**

4001 SW 47th Avenue • Suite 201 • Fort Lauderdale, Florida 33314 • Telephone: (954) 581-7500 • Fax: (954) 584-1442

AN  
  
ANDRX COMPANY

## Exclusivity Checklist

<b>NDA: 21-316</b>				
<b>Trade Name: Altacor Extended-Release Tablets</b>				
<b>Generic Name: Lovastatin</b>				
<b>Applicant Name: Aura Laboratories, Inc.</b>				
<b>Division: HFD-510</b>				
<b>Project Manager: William C. Koch, R.Ph.</b>				
<b>Approval Date: June 28, 2002</b>				
<b>PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?</b>				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
b. Is it an effectiveness supplement?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
If the answer to (d) is "yes," how many years of exclusivity did the applicant request? <b>three</b>				
<b>IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.</b>				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? NOTE: Approved NDA is for an immediate-release dosage form.	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
If yes, NDA # <b>19-643</b>				
Drug Name: <b>Mevacor</b>				
<b>IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.</b>				
3. Is this drug product or indication a DESI upgrade?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
<b>IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).</b>				

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes	X	No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes	X	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product	Mevacor			
NDA #	19-643			
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	X
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	X	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				

<p>2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.</p>					
<p>a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?</p>		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
<p>If "no," state the basis for your conclusion that a clinical trial is not necessary for approval <b>AND GO DIRECTLY TO SIGNATURE BLOCKS.</b></p>					
<p>Basis for conclusion:</p>					
<p>b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?</p>		Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
<p>1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.</p>		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
<p>If yes, explain:</p>					
<p>2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?</p>		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
<p>If yes, explain:</p>					
<p>c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:</p>					
Investigation #1, Study #:		146-009			
Investigation #2, Study #:		146-010			
Investigation #3, Study #:		146-011			
<p>3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.</p>					
<p>a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")</p>					
Investigation #1		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
Investigation #2		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
Investigation #3		Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
<p>If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:</p>					
Investigation #1 -- NDA Number					
Investigation #2 -- NDA Number					
Investigation #3 -- NDA Number					

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?			
Investigation #1	Yes	<input type="checkbox"/>	No <input checked="" type="checkbox"/>
Investigation #2	Yes	<input type="checkbox"/>	No <input checked="" type="checkbox"/>
Investigation #3	Yes	<input type="checkbox"/>	No <input checked="" type="checkbox"/>
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number			
Investigation #3 -- NDA Number			
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):			
Investigation #1	146-009		
Investigation #2	146-010		
Investigation #3	146-011		
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.			
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?			
Investigation #1	Yes	<input checked="" type="checkbox"/>	No <input type="checkbox"/>
IND#:			
Explain:			
Investigation #2	Yes	<input checked="" type="checkbox"/>	No <input type="checkbox"/>
IND#:			
Explain:			
Investigation #3	Yes	<input checked="" type="checkbox"/>	No <input type="checkbox"/>
IND#:			
Explain:			
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?			
Investigation #1	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
IND#:			
Explain:			
Investigation #2	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
IND#:			
Explain:			
Investigation #3	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
IND#:			
Explain:			

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	X
If yes, explain:				

*{See appended electronic signature page}*

\_\_\_\_\_  
Signature of PM

\_\_\_\_\_  
Date:

*{See appended electronic signature page}*

\_\_\_\_\_  
Signature of Division Director

\_\_\_\_\_  
Date:

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## Document Information Page

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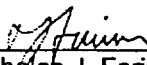
Exclusivity Statement

According to the information published in the "Approved Drug Products with Therapeutic Equivalence Evaluation, 20<sup>th</sup> edition, 2000" the reference listed drug, Mevacor® (Lovastatin) Tablets, marketed by Merck & Co., Inc. is entitled to a period of marketing exclusivity as shown below:

Exclusivity Code  
I-250

Exclusivity Expires  
March 11, 2002

Aura Laboratories, Inc.'s [ (lovastatin, USP) Extended-release Tablets will not be marketed for the ]

  
\_\_\_\_\_  
Nicholas J. Farina, Ph.D.      Date 2/28/01  
Vice President Regulatory Affairs

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ON ORIGINAL**

4001 SW 47th Avenue • Suite 201 • Fort Lauderdale, Florida 33314 • Telephone: (954) 581-7500 • Fax: (954) 584-1442

AN  
  
\_\_\_\_\_  
ANDRX COMPANY

Debarment Certification

On behalf of Aura Laboratories, Inc. a division of Andrx Pharmaceuticals, Inc., I hereby certify that we did not and will not use in any capacity the services of any individual, partnership, corporation, or associations debarred under sub-sections (a) or (b) of Section 306 of the Federal Food, Drug & Cosmetic Act in connection with NDA 21, 316 for        (Lovastatin, USP) Extended-Release Tablets.

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

2/1/01  
Date

**APPEARS THIS WAY  
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Financial Certification/Disclosure Statement

A signed Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) is attached.

Nicholas J. Farina, Ph.D.      2/1/01  
Nicholas J. Farina, Ph.D.      Date  
Vice President Regulatory Affairs

**APPEARS THIS WAY  
ON ORIGINAL**

**TEAM LEADER'S MEMO TO THE FILE**

**NDA 21-316**

**Drug Product: Altacor (Lovastatin extended-release) tablets**

**Date: January 23, 2002**

**Subject: Request by sponsor for tentative approval of \_\_\_\_\_  
indication derived from \_\_\_\_\_ data**

The sponsor submitted in their proposed labeling for Altacor, reference to the clinical trial data of \_\_\_\_\_  
\_\_\_\_\_ under the CLINICAL PHARMACOLOGY section, Clinical Studies subsection. An indication for \_\_\_\_\_ based on \_\_\_\_\_ data was also included in the proposed labeling under the INDICATIONS AND USAGE section.

Any indication or reference of lovastatin' efficacy based on \_\_\_\_\_ is approvable with this current submission. The proposed label is unacceptable as the sponsor has included \_\_\_\_\_ derived from \_\_\_\_\_ under the CLINICAL PHARMACOLOGY section that was not approved in the MEVACOR label. Specifically, the sponsor must delete \_\_\_\_\_  
- from \_\_\_\_\_ and the following two paragraphs:

In addition, approvability for this indication cannot be addressed until after Mevacor's exclusivity expiration date for this indication (September 11, 2002).

Mary H. Parks, MD  
Deputy Director  
Medical Team Leader HFD-510

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/s/  
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Mary Parks  
1/23/02 12:22:03 PM  
MEDICAL OFFICER

David Orloff  
1/30/02 10:39:17 AM  
MEDICAL OFFICER  
Concur with Dr. Parks

**APPEARS THIS WAY  
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**MEDICAL TEAM LEADER'S MEMO**

**NDA #:** 21-316

**Sponsor:** Aura Laboratories, Incorporated

**Name of Drug:** Altocor™ (lovastatin) extended-release tablets

**Dosage strengths:** 10, 20, 40, and 60 mg

**Indication:** lipid-altering therapy for patients with primary hypercholesterolemia and mixed dyslipidemia

**Date of Submission:** March 30, 2001

**Date Application Due:** January 30, 2002

**Primary Medical Reviewer:** Anne R. Pariser, MD

**Statistical Reviewer:** Joy Mele, MS

**BACKGROUND**

Lovastatin, an HMG-coA reductase inhibitor (statin), is a lipid-altering drug whose primary mechanism of action is the inhibition of the rate-limiting enzyme in cholesterol synthesis. The immediate-release formulation of lovastatin was approved in 1987 by the FDA as MEVACOR produced by Merck Research Laboratories. Currently available doses include 10 to 80 mg to be taken once daily. Treatment at these doses result in an approximate -21 to -40% lowering of LDL-C and -16 to -29% lowering of total-C. The effect of MEVACOR on the clinical course of atherosclerosis has also been evaluated in several studies including coronary angiographic studies, carotid B-mode ultrasound studies, and a 5-year placebo-controlled cardiovascular mortality and morbidity clinical trial. MEVACOR is indicated for the following:

1. to reduce the risk of MI, unstable angina, and coronary revascularization procedures in patients without clinically evident coronary heart disease but have average to moderately elevated total-C and LDL-C and below average HDL-C
2. to slow the progression of coronary heart disease
3. as an adjunct to diet and other nonpharmacological measures to reduce elevated total-C and LDL-C levels in patients with primary hypercholesterolemia

Statins, for the management of hypercholesterolemia, are effective and easily tolerated drugs whose use have also been associated with reductions in CV mortality and morbidity. The development of a statin formulation which could provide a more sustained inhibition of HMG-coA reductase activity has been postulated to result in improved lipid-altering efficacy at lower doses and decreased risk of safety concerns such as myopathy and elevations in hepatic transaminases. Aura Laboratories evaluated the effects of such a formulation for lovastatin in this new drug application for ALTOCOR at daily doses of 10, 20, 40 and 60 mg. In clinical pharmacokinetic studies with ALTOCOR compared to MEVACOR, it was observed that ALTOCOR had a prolonged T<sub>max</sub> and lower C<sub>max</sub> than MEVACOR. The AUC of lovastatin (prodrug) was higher with ALTOCOR but the lovastatin acid (active drug) concentrations were similar between ALTOCOR and MEVACOR.



This application was submitted as a 505(b)(2) application wherein some information required for its approval are from studies not conducted by or for Aura Laboratories and the sponsor has not obtained a right of reference to these studies. Aura Laboratories will rely on the Agency's finding of safety and effectiveness for the reference listed product, MEVACOR, from all preclinical studies and several clinical studies. The sponsor has conducted several clinical pharmacology studies to evaluate the pharmacokinetics of ALTOCOR and its relative bioavailability to MEVACOR. In addition, clinical studies of lovastatin extended-release were conducted by Aura Laboratories to support proposed labeling. These studies were the primary focus of the medical and statistical reviews as summarized in this team leader memo.

**SUPPORTIVE INFORMATION**

Data from 13 clinical studies were submitted to this new drug application. Ten of these were clinical pharmacology studies reviewed in detail by the Office of Clinical Pharmacology and Biopharmaceutics and summarized in tables 10 and 11 of Dr. Pariser's medical review. There were three clinical studies which provided the primary efficacy and safety data for ALTOCOR. These studies included:

Protocol 146-009

This was a randomized, double-blind, placebo-controlled, dose-response study evaluating the efficacy and safety of ALTOCOR 10, 20, 40, and 60 mg over 12 weeks of treatment.

Protocol 146-010

This was a randomized, double-blind, 2-way cross-over study comparing ALTOCOR 20 mg to MEVACOR 20 mg and ALTOCOR 60 mg to MEVACOR 60 mg. The total duration of the study was 34 weeks with two 12-week active treatment periods separated by a 6-week washout period. The study design is depicted in the following diagram from Dr. Pariser's review:

**Figure 1. Design of Protocol 146-010 from Dr. Pariser's review**

