NP: A1-316
Page 15
The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

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

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

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

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

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dL (see NCEP Guidelines above).
DATE: June 26, 2002

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

Don't hesitate to call with any questions.
Laurensia is a collaborative lowering agent derived from a species of *Laurensia*.

![Diagram of Laurensia](image)

Laurensia is used in white, non-photosensitive, opaque powders that are formulated in water and comes in a ready-to-use powder form.

Laurensia Tablets are supplied as 13 mg or 20 mg in 4 mg tablets for oral administration. Each tablet contains the following inactive ingredients: lactose monohydrate, stearic acid, and magnesium stearate. The tablets are indicated for the treatment of moderate to severe hyperlipidemia (Type IIa, IIb, and IV).

In clinical trials, Laurensia has been shown to lower LDL-C, triglycerides, and total cholesterol levels in a dose-dependent manner. The data presented in Table 1 show the percent changes in LDL-C and other lipid parameters for patients treated with Laurensia compared to placebo.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Cholesterol</th>
<th>LDL-C</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>120 ± 20</td>
<td>80</td>
<td>150</td>
</tr>
<tr>
<td>Laurensia</td>
<td>100 ± 15</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
</table>

**Table 1:** Percent Change from Baseline for Lipid Parameters

The effects of Laurensia on other lipid parameters are consistent with its mechanism of action and align with clinical guidelines for the management of hyperlipidemia.

For more information, please refer to the product’s full Prescribing Information and consult with your healthcare provider.
alimentation and to professional masseuses (measured using a simple appar-}

eau of the moment). The question was whether there was a significant

reduction in the frequency of erection response (in the absence of sexual

interest) in the form of possible measures. The results were

analyzed by the Kruskal-Wallis test and the Mann-Whitney U test.

The results of the study showed that there was no significant

difference in the frequency of erection response between the

groups, and no significant changes in the frequency of sexual

interest (in the absence of sexual interest) were observed.

In conclusion, the findings of the present study indicate that

professional masseuses do not have a significant effect on the

frequency of erections or sexual interest in men. Further

research is needed to investigate the possible impact of other

factors and populations on these outcomes.

References:


In the present study, the frequency of erection response was measured in men

before and after a course of sexual education. The frequency of erection response

was measured using a simple apparatus and the results were analyzed using

the Kruskal-Wallis test. The results showed that there was no significant

change in the frequency of erection response before and after the course of sexual

education. Therefore, it can be concluded that sexual education does not have

a significant impact on the frequency of erection response. Further research is

needed to investigate the possible impact of other factors and populations on

these outcomes.
Therapy of cholangiocarcinoma is a challenge, and overall survival is poor. Several patients with advanced or progressive disease may benefit from systemic treatment, such as chemotherapy. The following sections discuss the options available for the treatment of cholangiocarcinoma.

**Chemotherapy**

Various chemotherapy regimens have been evaluated in patients with cholangiocarcinoma. The most commonly used agents are 5-fluorouracil (5-FU) and cisplatin, and a combination of these drugs is often used as first-line therapy. Other agents, such as gemcitabine, doxorubicin, and mitomycin C, have also been studied. In a randomized trial comparing 5-FU and cisplatin with gemcitabine and cisplatin, there was no significant difference in overall survival between the two treatment groups. However, gemcitabine and cisplatin were associated with better response rates and fewer side effects. Therefore, gemcitabine and cisplatin is currently the standard of care for patients with advanced cholangiocarcinoma.

**Targeted Therapy**

Targeted therapies, such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors, have been evaluated in patients with cholangiocarcinoma. However, the efficacy of these agents is limited, and further studies are needed to determine their role in the treatment of this disease.

**Radiotherapy**

Radiotherapy may be considered as an adjuvant therapy for patients with resectable tumors. However, the role of radiotherapy in the treatment of cholangiocarcinoma is still under investigation.

**Supportive Care**

Supportive care is an important aspect of the treatment of cholangiocarcinoma. This includes managing symptoms such as pain, jaundice, and liver dysfunction. Palliative care, including the use of opioids and other pain medications, is crucial to improve the quality of life of patients with advanced disease.

**Clinical Trials**

Clinical trials are an important tool for evaluating new treatments for cholangiocarcinoma. Patients with advanced disease may be eligible for participation in clinical trials that are investigating new targeted therapies, immune checkpoint inhibitors, or combination therapies. Patients interested in participating in clinical trials should discuss their options with their healthcare provider.
WITHHOLD 60 PAGE (S)

Draft Labeling
Comments:
This is to confirm a scheduled telephone conference
to discuss your proposed package insert for NDA 21-316.

Date: January 07, 2002
Time: 11:00 AM

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

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

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

Pages (including this cover sheet): forty (40) in three transmissions
DATE: December 21, 2001

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

Comments:
This is to confirm a scheduled telephone conference
to discuss your proposed package insert for NDA 21-316.

Date: January 07, 2002
Time: 11:00 AM

Please supply a conference dial-in number so the Division
can phone you at the appointed time.
Please don’t hesitate to call with any questions.
NDA 21-316

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

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

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

We request that you conduct a drug interaction study comparing the pharmacokinetics of both lovastatin and lovastatin acid with and without concomitant antacid as a postmarketing study commitment. We request that this commitment adhere to the following timeline:

Final Report Submission: Within 12 months of the date of the action letter.

(The Division recommends that a draft protocol of this requested study be submitted to the application in time for the reviewer to provide comments.)

We also request that your commitment to perform this study, as requested, be submitted to the application as an amendment as soon as possible.

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

{See appended electronic signature page}

CLEARED FOR FAXING

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

APPEARS THIS WAY ON ORIGINAL
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/s/
William Koch
1/18/02 10:33:25 AM
CSO

Hae-Young Ahn
1/18/02 10:48:07 AM
BIOPHARMACEUTICS

APPEARS THIS WAY ON ORIGINAL
Comments:
Attached are comments from the Division regarding NDA 21-316. A response, submitted to this application, is required.

Please don’t hesitate to call with any questions.

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

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

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

01/18/02  12:33

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APPEARS THIS WAY ON ORIGINAL
March 30, 2001

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

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

Dear Sir/Madam:

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

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

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

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

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

Aura Laboratories, using both its own data and relying on sources permitted under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, proposes both to retain and to augment in several ways the labeling for the approved immediate-release product
Mevacor® (lovastatin tablets) which is a registered trademark of Merck & Company, Inc. as follows:

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

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

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

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

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

______ Development

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

• Experimental animal data involving controlled-release statin drugs;

• Favorable Phase 1 and 2 pharmacokinetic and clinical results, supporting continuation into Phase 3 studies; and

• Published Mevacor® data in the EXCEL Trial and in the FDA’s original medical officer review of Mevacor®, showing that the same total milligram dose of lovastatin is significantly more effective when administered twice-daily, rather than once-daily.
The development program, including the design of Phase 3 trials, was discussed with the Food and Drug Administration's Metabolic and Endocrine Division at an End-of Phase 2 Meeting, and during Phase 3. Aura's written correspondence with the FDA is included in this application.

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

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

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

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

Exclusivity

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

Patents and Exclusivity Covering Mevacor®

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

NDA No. 21-316 includes a "Paragraph III" certification concerning the '938 Patent', stating that Aura does not seek to market before the expiration of that patent.
Aura Laboratories, Inc. certifies that in accordance with 21 CFR 314.50(1)(3), a field copy of its New Drug Application, 505(b)(2) for Extended-Release Tablets 10, 20, 40, and 60 mgs was concurrently sent to FDA's Florida field office. The field copy is a true copy of the Chemistry, Manufacturing, and Controls technical sections contained in the Archival and Review copies of the application.

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

Sincerely,

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

Cc: Dr. David Orloff (cover letter only)
Ms. Margaret Simoneau (cover letter only)
Ms. Emma Singleton, Director, Florida District Office, Food and Drug Administration, 555 Winderley Place, Suite 200, Maitland, FL 32751 (cover letter and CMC section)
2. Revise the phase 4 commitment regarding regulatory criteria for water content and residual solvent in drug product revised to specify that the completed study will be provided to the application as a “Changes Being Effect in 30 Days” supplement and that the cover letter will state “Postmarketing Commitment - Study Final Report”.

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

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

Sincerely,

{See appended electronic signature page}

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

APPEARS THIS WAY
ON ORIGINAL
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/s/
------------------------
Enid Galliers
5/24/02 01:48:26 PM

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**Document Information Page**

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

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**Drafted by:** WCK/05.22.02  
**Revised by:** WMAdams05.22.02/SChung05.22.02/EGalliers05.24.02  
**Initialed by:** SMoore05.23.02/HYAhn05.24.02  
**Finalized:** WKoch05.24.02  
**Filename:** C:\WINDOWS\Desktop\NDA21316\LTRdrbph052502.doc

**DFS Key Words:**  
**Notes:** N000  
**Linking Instructions:** Link this letter to the incoming document containing the information requiring further clarification.

**END OF DOCUMENT INFORMATION PAGE**

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

Don’t hesitate to call with any questions.

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

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

Pages (including this cover sheet): Four(4)
# MESSAGE CONFIRMATION

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

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

---

**DATE:** May 24, 2002

---

**APPEARS THIS WAY ON ORIGINAL**

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**Comments:**

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

Don't hesitate to call with any questions.
TRANSMITTED BY FACSIMILE

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

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

Dear Dr. Farina:

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

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

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

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

APPEARS THIS WAY ON ORIGINAL
Nicholas J. Farina, Ph.D.
ANDRX LABORATORIES, INC.
NDA 21-316/MACMIS #10785

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

Sincerely,

(See appended electronic signature page)

Cheryl D. Cropp, Pharm.D., BCPS
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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

APPEARS THIS WAY
ON ORIGINAL
NDA 21-316

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

Dear Dr. Farina:

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

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

The following dissolution method and specification is recommended:

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

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<th>Time (hr)</th>
<th>Amount Dissolved (%)</th>
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</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
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<tr>
<td>8</td>
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We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.
If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

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

David Orloff
1/9/02 04:45:31 PM

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

Please don’t hesitate to call with any questions.

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

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

Pages (including this cover sheet): four (4)
DATE: January 09, 2002

APPEARS THIS WAY ON ORIGINAL

Comments:
Attached is a copy of correspondence from the Division regarding NDA 21-316. The original letter will be sent by mail. Please don't hesitate to call with any questions.
NDA 21-316

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

Dear Dr. Farina:

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

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

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

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

Sincerely,

(See appended electronic signature page)

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

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

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**DOCUMENT INFORMATION PAGE**

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**Linking Instructions:** Link this outgoing letter to all related IND and NDA incoming documents coded either PA (for the Proposed Pediatric Study Request) or PB (amendment to the Pediatric Written Request).

**END OF DOCUMENT INFORMATION PAGE**

The letter begins on the next page.

**APPEARS THIS WAY ON ORIGINAL**
NDA 21-316

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

Dear Dr. Farina:

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

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

1.

2.
WITHHOLD 2 PAGE (S)
9. Regarding the draft labeling:

(a) Revise the inactive ingredient list as follows:
1) revise "confectioner's sugar" to indicate the presence of "corn starch";
2) revise "synthetic iron oxides" to "synthetic black iron oxide" and "red iron oxide";
3) add "propylene glycol"; and
4) revise "PEGs" to "PEG 400" and "PEG 8000".
(b) Revise the proposed storage statement to use the USP definition of controlled room temperature (20-25°C) which is supported by the submitted stability studies.

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

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

Sincerely,

{See appended electronic signature page}

Stephen K. Moore, Ph.D.
Chemistry Team Leader I
Division of Metabolic and Endocrine Drug Products, HFD-510
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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

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

DATE: December 12, 2001

APPEARS THIS WAY  
ON ORIGINAL

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

Please don’t hesitate to call with any questions.

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

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

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

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN  
INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. IF YOU  
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PLEASE IMMEDIATELY NOTIFY US BY TELEPHONE (301-827-6430) AND RETURN IT TO US AT THE ABOVE THE ABOVE ADDRESS BY MAIL. THANK YOU!
Comments:
Attached is a copy of correspondence from the Division regarding NDA 21-316. The original letter will be sent by mail.

Please don’t hesitate to call with any questions.

TO: 
FROM:
NDA 21-316

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

Dear Dr. Farina:

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

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

1. Formulations used in clinical trials

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

2. Dissolution

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

1) justification of concentration of —— in dissolution medium,
2) comparison of paddle speed between 50 rpm and 75 rpm,
3) solubility in different pH media, and
4) dissolution profiles in different pH media.
If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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

APPEARS THIS WAY ON ORIGINAL
NDA 21-316

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

Dear Dr. Farina:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Jovastatin extended-release) Tablets, 10, 20, 40, 60 mg

Review Priority Classification: Standard (S)

Date of Application: March 30, 2001

Date of Receipt: March 30, 2001

Our Reference Number: NDA 21-316

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 29, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be January 30, 2002, and the secondary user fee goal date will be March 30, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55, please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans
Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our website at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

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

If you have any questions, call me at (301) 827-6411.

Sincerely,

[See appended electronic signature page]

Margaret Simoneau, R.Ph.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
/s/
Margaret Simoneau
4/5/01 12:56:05 PM

APPEARS THIS WAY ON ORIGINAL
**Application # (s):** NDA 21-316  
**Document Type:** NDA Letter  
**Document Group:** Acknowledgement Letters  
**Document Name:** NDA Acknowledgement Letter  
**Letter Code:** NDA-A1  

**COMIS Decision:** No Decision Code  
*(ACKNOWLEDGEMENT)*  

**Drafted by:** ddk/April 4, 2001  
**Revised by:** Keels/April 4, 2001  
**Initiated by:** Simoneau 4.4.01/Galliers 4.4.01  
**Finalized:** Ddk/April 4, 2001  
**Filename:** 21316AC.DOC  

**DFS Key Words:**  

**Notes:**  

**Linking Instructions:** Link the outgoing letter to the original 000 incoming document for the NDA.
Meeting Minutes
Division of Metabolic and Endocrine Drug Products
NDA 21-316

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

Time: 9:30 to 10 AM

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

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

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

Post Meeting Notes:

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

2. ("

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

Concurrence Chairman: Dr. Parks (See appended signature page)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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

APPEARS THIS WAY ON ORIGINAL
Meeting Minutes

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

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

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

1. Meeting Objective

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

2. Discussion and Conclusions

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

Minutes preparer: M. Simoneau

Concurrence Chairman: D. Orloff

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

APPEARS THIS WAY ON ORIGINAL
NO ADVISORY COMMITTEE MEETING
Electronic Mail Message

Date: 7/3/01 1:14:12 PM
From: Sammie Beam 301-827-3231 FAX 3 (BEAMS8A1)
To: WILLIAM C KOCH JR (FDACD) (KOCWH8A1)
Subject: OPDRA consult #01-0148 for NDA 21-316

Hello,

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

Thanks,
Sammie Beam
REQUEST FOR CONSULTATION

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<td>NAME OF FIRM: Aura Laboratories Inc.</td>
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REASON FOR REQUEST

I. GENERAL
- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING/CHANGE/ADDITION
- MEETING PLANNED BY

II. BIOMETRICS
- STATISTICAL EVALUATION BRANCH
  - TYPE A OR B NDA REVIEW
  - END OF PHASE II MEETING
  - CONTROLLED STUDIES
  - PROTOCOL REVIEW
  - OTHER

- STATISTICAL APPLICATION BRANCH
  - CHEMISTRY REVIEW
  - PHARMACOLOGY
  - BIOPHARMACEUTICS
  - OTHER

III. BIOPHARMACEUTICS
- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES

IV. DRUG EXPERIENCE
- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS/List below
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

V. SCIENTIFIC INVESTIGATIONS
- CLINICAL
- PRECLINICAL

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

SIGNATURE OF REQUESTER | METHOD OF DELIVERY (Check one) | SIGNATURE OF DELIVERER
|                      | MAIL | X HANDB |
|                      |      |        |

Consult.088

Team Leader Concurrence: ____________________________ Date

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

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ON ORIGINAL
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Application #(s): NDA 21-316
Document Type: FORMS
COMIS Decision:

Drafted by: WKoch/06.26.01
Revised by:
Initialed by:
Finalized: WKoch/.00
Filename: C:/Windows/Desktop/NDA 21316/CNopdra062601.doc

DFS Key Words:

Notes: 06.08.01

Linking Instructions:

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APPEARS THIS WAY
ON ORIGINAL
June 8, 2001

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

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

Dear Sir:

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

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

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

Sincerely,

[Signature]
Nicholas J. Farina, PhD
Vice President, Regulatory Affairs
REQUEST FOR CONSULTATION

TO (Division/Office): HFD-410 OPDRA
FROM: HFD-510 Metabolic and Endocrine Drug Products

Date: 1/12/01
IND NO. —
NDA NO. —

NAME OF DRUG: Livanex Tablets
PRIORITY CONSIDERATION: NDA Submission in March 2001
CLASSIFICATION OF DRUG: Lipid/Filtering
DESIRED COMPLETION DATE: February 28, 2001

NAME OF FIRM:

REASON FOR REQUEST:

I. GENERAL

☐ NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY

☐ PRE-NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER (SPECIFY BELOW):

TRADEMARK REVIEW

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

☐ TYPE A OR B NDA REVIEW
☐ END OF PHASE II MEETING
☐ CONTROLLED STUDIES
☐ PROTOCOL REVIEW
☐ OTHER (SPECIFY BELOW):

STATISTICAL APPLICATION BRANCH

☐ CHEMISTRY REVIEW
☐ PHARMACOLOGY
☐ BIOPHARMACEUTICS
☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

PHASE IV SURVEILLANCE/EPIEMIOLOGY PROTOCOL
DRUG USE e. g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
CASE REPORTS OF SPECIFIC REACTIONS (List below)
COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL
☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the enclosed submission (6 copies).
If there are any questions please contact:
Chemist - Sharon Kelly, Ph.D. 301-768-5494
Pharm Manager - Margaret Semmes 7-6411

NATURE OF REQUESTER: /S/

NATURE OF RECEIVER: /S/

METHOD OF DELIVERY (Check one)
☐ MAIL
☒ HAND

SIGNATURE OF DELIVERER:

Chemistry Team Leader: /S/
January 8, 2001

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

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

Dear Sir:

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

Nicholas J. Farina, PhD
Vice President, Regulatory Affairs