

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA-21-316

APPROVAL LETTER



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:

Please refer to your new drug application (NDA) dated March 30, 2001, received March 30, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Altocor (lovastatin) Extended-Release Tablets, 10 mg, 20 mg, 40 mg, 60 mg.

We acknowledge receipt of your submissions dated May 1, 17, and 28, 2002. Your submission of May 1, 2002, constituted a complete response to our April 18, 2002, action letter.

This new drug application provides for the use of Altocor, an extended release formulation of lovastatin, for lowering total cholesterol and LDL-C to target levels as an adjunct to diet and exercise, to slow the progression of atherosclerosis in patients with coronary heart disease, and to reduce Total-C, LDL-C, Apo B and triglycerides and to increase HDL-C in patients with Fredrickson types IIa and IIb dyslipoproteinemia.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted February 18, 2002, immediate container and carton labels submitted May 17, 2002). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-316." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submissions dated May 1 and 28, 2002. These commitments are listed below.

1. Commitment/Study Description: A drug interaction study comparing the pharmacokinetics of both lovastatin and lovastatin acid with and without concomitant antacid.

Commitment Category: Biopharmaceutics

Protocol Submission: The Division recommends that a draft protocol for this study be submitted to the application for review and comment and that the protocol not be initiated until comments have been communicated.

Final Report Submission: within 12 months of final approval.

2. Commitment/Study Description: An analysis for percent water content and residual solvent using the methods in STM AR-013 for at least the first three commercial drug product lots of each strength in order to revise or maintain the acceptance criteria submitted as a "Changes Being Effected in 30 Days" supplement.

Commitment Category: Chemistry, Manufacturing and Controls

Final Report Submission: within three months of final approval.

3. Commitment/Study Description: Establishment of in-process weight increase specifications for the seal, enteric and sustained release coating process steps based on three post-approval commercial drug product lots of each strength submitted as a "Changes Being Effected in 30 Days" supplement. This commitment also provides for increased sampling for dissolution testing on all lots released for marketing in the interim.

Commitment Category: Chemistry, Manufacturing and Controls

Final Report Submission: within three months of final approval.

Submit protocols for requested studies and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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). We are waiving the pediatric study requirement for this application for patients <10 years old and deferring submission of pediatric studies for patients 10-17 years old. If we determine that pediatric studies are necessary, we will specify a date by which you must submit the required assessments.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call 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
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**APPEARS THIS WAY
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/s/

David Orloff
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-316

APPROVABLE LETTER

4.18.02



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-316

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

Dear Dr. Farina:

Please refer to your new drug application (NDA) dated March 30, 2001, received March 30, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Altocor (lovastatin extended-release) Tablets, 10 mg, 20 mg, 40 mg, 60 mg.

We acknowledge receipt of your submissions dated February 4 and 18, March 21, and April 10, 2002. Your submission of February 18, 2002, constituted a complete response to our January 30, 2002, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

CHEMISTRY, MANUFACTURING, AND CONTROLS

1. 

2.



5. Regarding labeling:

Either submit appropriate labels and labeling for the packaging configurations listed below or confirm that these configurations are no longer proposed for approval in the NDA:

- (1) count packages of 10, 20, 40, and 60 mg tablets; and
- (2) - count packages for 10 and 20 mg tablets.

6. Regarding dissolution method and specifications:

Provide the results of testing on the NDA drug product lots using the dissolution procedure and criteria recommended in item #7 below.

BIOPHARMACEUTICS

7. The dissolution method and specifications should be modified as follows:

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 based on level 2, USP XV:

Time (hr)	Amount Dissolved (%)
2	<u> </u>
8	<u> </u>
16	<u> </u>

If additional information relating to the safety or effectiveness of this drug becomes available, submit it to the application as an amendment.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

In addition, we provide the following comments from the chemistry reviewer. These are not issues that needed to be resolved before the NDA can be approved.

1. We acknowledge your commitment to revise the batch production records to delete the _____ statements and request that the revised documents be submitted in the annual report.
2. We recommend that following items be included in the batch production record and that the revised document be submitted in the first annual report:
 - (a) the actual _____ and
 - (b) the tablet _____ limits.
3. We accept your justification regarding stability studies for the _____ count packages of 60 mg tablets. The initial post approval lots of 60 mg tablets in these packages should be placed on stability and the results submitted in the first annual report.
4. We acknowledge your commitment to monitor data for the first 50 API batches and re-evaluate the adequacy of the acceptance specifications.
5. Provide a copy of the master packaging record (MPR) for the 250 cc bottle with _____ and the 500 cc bottle with _____ packaging configurations. Alternatively, specify that the previously submitted packaging process and controls with appropriate changes in the packaging components will be used. The revised MPRs should be included in the first Annual Report (AR).

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call 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
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
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We acknowledge receipt of your submissions dated April 16, June 8, July 26, September 26, and October 10 and 29 (2), 2001, and January 8 and 30, 2002.

We also acknowledge receipt of your submission dated January 21, 2002. This submission was not reviewed for this action. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

CHEMISTRY, MANUFACTURING, AND CONTROLS

1.



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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.

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If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a re-tabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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