CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-316

CHEMISTRY REVIEW(S)

NDA 21-316

ALTOCOR™ (lovastatin) Extended-Release Tablets 10, 20, 40, 60 mg

Aura Laboratories, Inc.

Mike Adams
DMEDP, HFD-510

Table of Contents

Chemistry Review Data Sheet

21-316

1. NDA ~~31-316~~

2. REVIEW #4

3. REVIEW DATE: 05/29/02

4. REVIEWER: Mike Adams

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	03/30/01
Correspondence	10/29/01
CMC Review #1	11/02/01
CMC Review #2	11/27/01
DR (CMC) Letter	12/11/01
Amendment	01/21/02
AE Letter	01/30/02
Amendment	02/18/02
CMC Review #3	03/20/02
CMC Review #3/biopharm conclusion	04/08/02
CMC Review #3/amendment	04/17/02
AE Letter	04/18/02
Telephone Conference	04/25/02
DR Letter	05/24/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	05/01/02
Amendment	05/28/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Aura Laboratories, Inc.
Address:	401 Hackensack Avenue 9th Floor Hackensack, NJ 07601
Representative:	Nickolas J. Farina, Ph.D. Vice President, Regulatory Affairs
Telephone:	610-428-2417

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

a) Proprietary Name: ALTOCOR™
b) Non-Proprietary Name (USAN): Lovastatin Extended Release Tablets
c) Code Name/# (ONDC only): none
d) Chem. Type/Submission Priority :
Chemical Type: 1RS
Submission Priority: 3S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: treatment of hyperlipidemia

11. DOSAGE FORM: extended release tablets

12. STRENGTH/POTENCY: 10, 20, 40, 60 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS [Note27]: No

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: USP 24

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]				3	Adequate	See comments under in CMC Review #1	—
				3	Adequate		—
				3	Adequate		—
				3	Adequate		—
				3	Adequate		—
				3	Adequate		—
				3	Adequate		—

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND [redacted] HFD-510)	Aura	ER tablets

CHEMISTRY REVIEW

Chemistry Review Data Sheet

IND ——(HFD-120)	Aura	ER tablets
NDA 19-643 (HFD-120)	Merck	IR tablets (RX)
NDA		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	—		
EES	Acceptable by OC	06/08/01 & 06/29/01	OC
Pharm/Tox	—		
Biopharm	Accepted with comment	05/11/02	S.Chung
LNC	—		
Methods Validation	To be sent		M.Adams
OPDRA	—		
EA	Excluded		M.Adams
Microbiology	—		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-316

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC information in the proposed application is adequate to support APPROVAL (AP).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following phase 4 commitments for CMC information have been proposed and accepted as adequate to support APPROVAL of the proposed application:

1. Andrx will revise the batch production records (BPRs) to delete the ——————— statements and will submit the revised documents in the first annual report (AR).
2. Andrx will include the following information, already specified in the application, into the BPRs and submit them in the first AR:
   (a) [- -] and
   (b)
3. Andrx will place the initial post approval lots of 60 mg tablets in the — count and — count packages on stability and the results will be submitted in the first AR.
4. Andrx will monitor data for the first 50 drug substance lots and re-evaluate the adequacy of the acceptance specifications and submit any changes to the application as appropriate.
5. Copies of the master packaging record for 250 cc bottle with ——————— and 500 cc bottle with ——————— configurations will be submitted in the first AR.
6. Andrx will establish in-process weight increase specifications for the seal, enteric and sustained release coating processes, and submit a CBE-30 supplement within 3 months of application approval.
7. Andrx will obtain %water content and residual solvent data and submit a CBE-30 supplement to either maintain or revise the current regulatory criteria within 3 months of application approval.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG PRODUCT

Altocor™ tablets contain 10, 20, 40 and 60 mg of the pro-drug lovastin, USP in an extended release formulation intended for the

treatment of hyperlipidemia. The active moiety is the β-hydroxy acid form of lovastin. The product will be distributed initially as a — count market package for each strength and a — count physician sample package for the 60 mg strength.

The tablet configuration and film coatings for the extended release dosage form were developed under IND ——— (HFD-510) and IND —— (HFD-120), and are described in patent 5,916,595. The dosage form is composed of an extended release core, a seal coating for ——————— an enteric coating, a sustained release coating and ——————————— In-process specifications for film coating weight are to be established under a phase 4 commitment and submitted as a CBE-30 supplement. The tablets are waxed and imprinted. The 10 mg and 20 mg tablets weight 167 mg each. The 40 mg and 60 mg tablets weigh 328 mg each.

Detailed unit and batch composition statements are provided. The only non-USP/NF ingredients are ——————————— ——————————— Ingredient controls are described in detail and the suppliers are identified. Tablet manufacture, packaging, process control testing and regulatory testing are performed by Andrx Pharmaceuticals and — contract laboratories. The proposed manufacturing and control sites were found acceptable by OC as of 06/29/01.

The submitted production and packaging batch records for the commercial process and executed batch records for the NDA tablet lots address each proposed tablet strength and packaging configuration. The proposed IP and QC manufacturing controls are described in detail. The NDA proposes a — batch scale-up upon approval and includes supporting data and information as specified in the SUPAC MR guidance. The sampling plan, tests, methods and acceptance criteria for product release testing are described in detail and are adequate regulatory purposes. The adequacy of the accepted regulatory criteria for water content and residual solvents will be investigated further under a phase 4 commitment with the results submitted as a CBE-30 supplement. Release testing includes identity, assay, uniformity, dissolution, organic impurities and residual solvents ——————————— The assay method and ——— ——— are used for identity testing. Assay, uniformity, purity and dissolution use an ——————— method. Residual organic solvents are determined by —— method. Complete method validation studies are provided for each regulatory method. The impurity methods are shown to adequately detect and quantitate the known impurities and degradants. Impurity and degradation profiles were established during NDA development, and from chemical and light stress studies. Impurities are shown to be from ——————— ——————————— Most degradants are from the drug substance and the most prevalent degradant is the active moiety. There are no microbiology issues in this dosage form.

Each proposed container/closure system consists of a — bottle with ——— cotton filler and ——— . Detailed descriptions and acceptance criteria are provided for each packaging component. Each packaging configuration has been shown to be suitable for its intended use.

ICH room temperature and accelerated condition stability studies are provided on 9 developmental batches representing each tablet strength and each packaging configuration. The firm has justified an initial expiry period of 24 months at USP room temperature. The post approval stability protocol is acceptable.

CMC information on the submitted carton and container labels, and package insert labeling meets the requirements of 21 CFR 201.56 and 201.57.

The applicant requests a categorical exclusion under 21 CFR 25.31 in that the proposed drug product is to be a replacement dosage form.

DRUG SUBSTANCE

——— is provided by ——— This material has already been approved for use in — Merck applications; NDA 19,643 (10 mg, 20 mg and 40 mg immediate release Mevacor™ tablets for Rx use) ——— . Complete and adequate information regarding ——— ——— profile is provided in ——— type II DMF ——— The DMF was previously found acceptable for CMC information and not reviewed for this application. Bulk lovastatin is [ ]

The NDA acceptance specifications are USP monograph testing for molecular and enantiomeric identity; inorganic and organic purity; and assay plus ——— and residual solvents. No previously unreported impurities are indicated in the application. Regulatory tests, methods and acceptance criteria are described in detail in the NDA. ——— methods are used for assay ——— , impurities ——— and residual solvents ——— The impurity methods are shown to detect and quantitate the known impurities and degradants. Identity testing is by the assay method and ——— . Complete and adequate method validation studies are provided for each regulatory method.

Stress stability studies demonstrate that bulk material can be stored ———

B. Description of How the Drug Product is Intended to be Used

Altocor™ is intended to provide 10 mg, 20 mg, 40 mg or 60 mg of lovastin in a once a day oral dose for extended periods concomitant with a standard cholesterol-lowering diet. The initial market package will be a — count bottle. Once ingested, lovastin is hydrolyzed into its active β-hydroxyacid form and acts as an inhibitor of HMG-CoA reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate which is a rate-limiting step in the synthesis of cholesterol.

C. Basis for Approvability or Not-Approval Recommendation

The application is APPROVABLE from the CMC perspective. The applicant has addressed all outstanding review issues.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist	M.Adams/05-29-02
ChemistryTL	S.Moore/05-29-02
PM	W.Koch

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 14 PAGE (S)

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/s/

Mike Adams
5/29/02 06:14:06 PM
CHEMIST

Stephen Moore
5/29/02 06:36:37 PM
CHEMIST

MEMORANDUM

DATE 04/17/02
FROM Mike Adams, HFD-820
TO NDA 21-316

RE: Revision to CMC Review #3, section H: List of Chemistry Deficiencies and Comments

1. The following deficiency and phase 4 commitment resulted from Response 7(b):

* Deficiency: Regarding your phase 4 commitment to submit USP <671> data prior to drug product distribution, please revise this commitment to provide for the submission of a CBE-30 supplement and to specify a due date for the submission.

* Phase 4 Commitment: The firm commits to repeat the USP <671> testing with the [redacted] removed for each container/closure combination and to submit the data as a CBE supplement prior to DP distribution. [Request for a CBE-30 submission and submission date in CMC Review #2.]

It was decided that a phase 4 commitment to submit a CBE supplement after NDA approval, but before drug product distribution, could not be accepted.

The request was intended to obtain packaging qualification data. Specifically, I wanted to address [redacted] provided by the bottle/closure during time of patient use (with the [redacted] removed). [redacted] during long term storage (with the [redacted] in place) had already been addressed.

The tablets have been established to be somewhat [redacted] therefore adequate protection through time of use is necessary. The PI indicates dosing is 1 tablet/day for an extended period, thus tablet count equals the number of days the bottle will be used without the [redacted] in place. Policy is to consider packages holding less than 3 months drug product as not having a [redacted] issue unless the product is very [redacted] The [redacted] count (patient) packages clearly fall under the threshold. The [redacted] count [redacted] package clearly falls above the threshold. It was decided that the 90 count (patient) package falls above the threshold in that this is likely to be the only patient package approved under the NDA.

The comment was revised to the following:
We cannot accept your commitment to submit USP <671> data for bottles with the ——— removed as a CBE supplement after NDA approval, but before drug product distribution. This data for the 90 and —— count packages should be submitted prior to NDA approval. Data for the ——————— count packages can be provided to the application in the annual report.

2. Likewise, the firm stated in phase 4 commitment 2 regarding the revision of BPRs, that a CBE supplement will be submitted prior to drug product distribution. The firm is to be advised that the revised BPRs should be instead submitted in the first annual report.

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/s/

Mike Adams
4/17/02 06:12:18 PM
CHEMIST

Stephen Moore
4/17/02 06:14:50 PM
CHEMIST

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ON ORIGINAL

CDER CHEMISTRY REVIEW CDER

NDA 21-316

ALTOCOR™ (lovastatin) Extended-Release Tablets 10, 20, 40, 60 mg

Aura Laboratories, Inc.

Mike Adams
DMEDP, HFD-510

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review Data Sheet

1. NDA ~~31-316~~ 21-316

2. REVIEW #3 AMENDMENT

3. REVIEW DATE: 04/08/02

4. REVIEWER: Mike Adams

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	03/30/01
Correspondence	10/29/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	01/21/02
Amendment	02/18/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Aura Laboratories, Inc.
Address:	401 Hackensack Avenue 9th Floor Hackensack, NJ 07601
Representative:	Nickolas J. Farina, Ph.D. Vice President, Regulatory Affairs
Telephone:	610-428-2417

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ALOCOR
b) Non-Proprietary Name (USAN): Lovastain Extended Release Tablets
c) Code Name/# (ONDC only): none
d) Chem. Type/Submission Priority (ONDC only):
Chemical Type: 1RS
Submission Priority: 3S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: treatment of hyperlipidemia

Chemistry Review Data Sheet

11. DOSAGE FORM: extended release tablets

12. STRENGTH/POTENCY: 10, 20, 40, 60 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: USP 24

17. RELATED/SUPPORTING DOCUMENTS: See Review #3

18. STATUS: See Review #3

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-316

The Executive Summary

I. Recommendations: Unchanged from Review #3

II. Summary of Chemistry Assessments See Review #3

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: M.Adams/04-08-02
ChemistryTL/Date: S.Moore/
PM Name/Date: W.Koch/

CC Block

APPEARS THIS WAY
ON ORIGINAL

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/s/

Mike Adams
4/16/02 08:43:17 AM
CHEMIST

Stephen Moore
4/16/02 12:19:17 PM
CHEMIST

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CHEMISTRY REVIEW

NDA 21-316

ALTOCOR™ (lovastatin) Extended-Release Tablets 10, 20, 40, 60 mg

Aura Laboratories, Inc.

Mike Adams
DMEDP, HFD-510

APPEARS THIS WAY
ON ORIGINAL

Table of Contents

Chemistry Review Data Sheet

1. NDA ~~31-316~~ 21-316

2. REVIEW #3

3. REVIEW DATE: 03/20/02

4. REVIEWER: Mike Adams

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	03/30/01
Correspondence	10/29/01

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	01/21/02
Amendment	02/18/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Aura Laboratories, Inc.
Address:	401 Hackensack Avenue 9th Floor Hackensack, NJ 07601
Representative:	Nickolas J. Farina, Ph.D. Vice President, Regulatory Affairs
Telephone:	610-428-2417

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ALOCOR
b) Non-Proprietary Name (USAN): Lovastain Extended Release Tablets
c) Code Name/# (ONDC only): none
d) Chem. Type/Submission Priority (ONDC only):
Chemical Type: 1RS
Submission Priority: 3S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: treatment of hyperlipidemia

11. DOSAGE FORM: extended release tablets

12. STRENGTH/POTENCY: 10, 20, 40, 60 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: USP 24

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
				3	Adequate	See comments under	—
				3	Adequate	—	—
				3	Adequate	—	—
				3	Adequate	in CMC Review #1	—
				3	Adequate		—
				3	Adequate		—
				3	Adequate		—

Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND — (HFD-510)	Aura	ER tablets
IND — (HFD-120)	Aura	ER tablets
NDA 19-643 (HFD-120)	Merck	IR tablets (RX)
NDA [redacted]	[redacted]	[redacted]

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	06/29/01	MAdams
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	To be sent		
OPDRA			
EA	N/A		
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-316

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE (AE) pending resolution of the CMC issues listed in section H of the Chemistry Assessment.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Except for the requested revisions, the proposed phase 4 commitments are ADEQUATE to support NDA approval.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

DRUG SUBSTANCE

The proposed [redacted] USP provided by [redacted] This material has already been approved for ~ Merck applications; NDA 19,643 is 10, 20, 40 mg IR tablets (Mevacor□) for Rx use and [redacted] Information regarding [redacted] and [redacted] is provided in [redacted] type II DMF [redacted] are reported for this material.

The NDA acceptance specifications are USP monograph testing for molecular and enantiomeric identity; inorganic and organic purity; and assay plus [redacted] and residual solvents. No new impurities were reported in this application. Tests, methods and acceptance criteria are described in detail in the NDA. [redacted] methods are used for assay [redacted], impurities [redacted], and residual solvents [redacted] The impurity method is shown to detect and quantitate the known impurities and degradants. Identity testing is by the assay method and [redacted] Method validation studies are provided for each regulatory method.

Stress stability studies indicate that bulk material can be stored [redacted]

DRUG PRODUCT

The proposed drug product is 10,20,40,60 mg modified release tablets developed under IND [redacted] (HFD-510) and IND

——— (HFD-120). The dosage form is composed of an extended release core ———————, a coating for ——— ——— an enteric coating ——————— ——————— , a sustained release coating ——————— ——————— and ——————— which is then waxed and imprinted. The 10,20 mg tablets weight 167 mg and the 40,60 mg tablets weigh 328 mg. Detailed unit and batch composition statements are provided. The only non-USP/NF ingredients are ——————————— and the ——— Ingredient controls are described in detail and the suppliers are identified.

Tablet manufacture, packaging, process control testing and regulatory testing are performed by Andrx Pharmaceuticals and — contract laboratories. The proposed manufacturing and control sites were found acceptable by OC as of 06/29/01.

The submitted production and packaging batch records for the post approval process and executed batch records for the NDA tablet lots address each proposed tablet strength and packaging configuration. The proposed IP and QC manufacturing controls are described in detail. The NDA proposes and supports a — batch scale-up upon approval with the data and information specified in the SUPAC MR guidance. The sampling plan, tests, methods and acceptance criteria for product release testing are described in detail. Release testing includes identity, assay, uniformity, dissolution, organic impurities and residual solvents ——————————— The assay method and ——— are used for identity testing. ——— methods are used for assay, uniformity, purity, dissolution ——— and residual organic solvents — testing. Complete method validation studies are provided for each regulatory method. The impurity methods are shown to adequately detect and quantitate the known impurities and degradants. Impurity and degradation profiles were established during NDA development, and from chemical and light stress studies. Impurities are found to be from ——— ——————— Most degradants are from the drug substance. There are no microbiology issues in this dosage form.

The proposed packaging configurations are a — count physician sample; —— 90 count patient packages; and a —— count pharmacy pack. Each container/closure system consists of a ——————————— cotton filler and ——————————— ——— Detailed descriptions and acceptance criteria are provided for each packaging component. Each packaging configuration has been shown to be suitable for its intended use.

ICH room temperature and accelerated condition stability studies are provided on 9 developmental batches representing each tablet strength and each packaging configuration. The firm proposes an initial expiry period of 24 months at USP room temperature. The postAP protocol is acceptable.

CMC information on the submitted carton and container labels, and package insert labeling meets the requirements of 21 CFR 201.56 and 201.57.

The applicant requests a categorical exclusion under 25.31 as the proposed drug product is to be a replacement dosage form.

B. Description of How the Drug Product is Intended to be Used

Treatment of Hyperlipidemia

C. Basis for Approvability or Not-Approval Recommendation

The application is APPROVABLE (AE) pending resolution of the following CMC issues:

1. The proposed tablet manufacturing process controls need to be finalized.
2. The acceptance criteria for impurities and residual solvents based on submitted test data needs to be finalized.
3. The phase 4 commitments regarding the manufacturing process and controls, packaging qualification studies, and labels and labeling need additional refinements; see list after draft letter.
4. The dissolution test needs to be finalized so that a conclusion can be reached for the proposed drug product shelflife.

The draft letter in section H of the CMC Assessment lists to the comments and deficiencies to be submitted to the firm.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:	M.Adams/03-20-02
ChemistryTL/Date:	S.Moore/
PM Name/Date:	W.Koch/

C. CC Block

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/s/

Mike Adams
4/16/02 08:39:43 AM
CHEMIST

Stephen Moore
4/16/02 12:14:34 PM
CHEMIST

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DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS, HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 21-316 **CHEM.REVIEW #2** **REVIEW DATE:** 11/27/01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	03/30/01	03/10/01	07/17/01
Correspondence	10/29/01	10/30/01	---

NAME & ADDRESS OF APPLICANT:
Aura Laboratories, Inc.
401 Hackensack Avenue
9th Floor
Hackensack, NJ 07601

DRUG PRODUCT NAME
PROPRIETARY: Altocor™
NONPROPRIETARY: Lovastatin XL [Lovastatin, USP Extended Release Tablets]
CODE NAME: none
CHEMICAL TYPE/THERAPEUTIC CLASS: 3S
PHARMACOL CATEGORY/INDICATION: treatment of hyperlipidemia
DOSAGE FORM: 'extended-release' tablet
STRENGTH: 10,20,40,60 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: Rx
CHEMICAL NAME/STRUCTURE, MOLECULAR FORMULA/WEIGHT: USP 24
SPECIAL PRODUCT: No
SUPPORTING DOCUMENTS: See CMC Review #1
DOCUMENTS SUPPORTED BY THIS FILE: None
RELATED DOCUMENTS: See CMC Review #1
CONSULTS:
Biopharm: submitted by CSO; pending
EER: submitted by initial reviewer; completed
Trademark: submitted by CSO; pending
REMARKS/COMMENTS: Reviewed are the container labels and the updated stability studies.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:
The proposed application is still APPROVABLE (AE) pending resolution of the CMC issues listed in section H of this review. The revised CMC comments should be forwarded to the applicant as an INFORMATION REQUEST (IR) letter.

Mike Adams
Review Chemist, HFD-820

Steve Moore
Chemistry Team Leader, HFD-820

cc:
NDA 21-316
HFD-510/div file
HFD-510/W.Koch/CSO
HFD-820/M.Adams/CMC/11-27-01
R/D Initial: S.Moore/11- -01
Filename: c:\my documents\21316111.doc.2MA

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/s/

Mike Adams
11/27/01 06:08:02 PM
CHEMIST

Stephen Moore
12/5/01 05:25:06 PM
CHEMIST

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ON ORIGINAL

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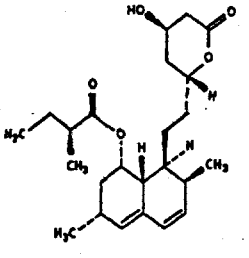
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS
HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 21-316 **CHEM.REVIEW #1** **REVIEW DATE:** 11/02/01

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	03/30/01	03/10/01	07/17/01

NAME & ADDRESS OF APPLICANT:
Aura Laboratories, Inc.
401 Hackensack Avenue
9th Floor
Hackensack, NJ 07601

DRUG PRODUCT NAME
PROPRIETARY: ————————
NONPROPRIETARY: Lovastatin XL [Lovastatin, USP Extended Release Tablets]
CODE NAME: none
CHEMICAL TYPE/THERAPEUTIC CLASS: 3S
PHARMACOLOGICAL CATEGORY/INDICATION: treatment of hyperlipidemia
DOSAGE FORM: extended release tablet
STRENGTH: 10,20,40,60 mg
ROUTE OF ADMINISTRATION: oral
DISPENSED: Rx



CHEMICAL NAME/STRUCTURE, MOLECULAR FORMULA/WEIGHT: USP 24

APPEARS THIS WAY
ON ORIGINAL

SPECIAL PRODUCT: NO

SUPPORTING DOCUMENTS

DMF#	HOLDER	ITEM PROVIDED	LOA DATE	STATUS
[redacted]			12/12/99	Adequate
			10/18/00	Adequate
			07/27/99	Adequate
			02/12/99	Adequate
			03/12/98	Adequate
			09/03/99	Adequate
			04/04/00	Adequate

DOCUMENTS SUPPORTED BY THIS FILE: None

RELATED DOCUMENTS

FILE	HOLDER	DRUG PRODUCT	REVIEW DIVISION
IND [redacted]	Aura	extended release tablets	HFD-510
IND [redacted]	Aura	extended release tablets	HFD-120
NDA 19,643	Merck	Mevacor® IR tablets (Rx)	HFD-120
NDA [redacted]	[redacted]	[redacted]	[redacted]

CONSULTS

Biopharm: submitted by CSO; pending
EER: submitted by initial reviewer; completed
Trademark: submitted by CSO; pending

REMARKS/COMMENTS

The firm has submitted this NDA under section 505(b)(2) for an extended-release version of an existing immediate release DP (Merck's Mevacor®, NDA 19-643). The proposed DP is to be used for patients with dyslipidemia who are at risk of atherosclerotic vascular disease. There is currently no controlled release product on the market. They intend to retain and extend the Mevacor® labeling. Aura proposes a 3 year exclusivity for this DP based on (1) new dosage form (extended release) and (2) use of controlled release dosage form for the "original" indications. The firm notes that [redacted] XL® has not been marketed in the US or any foreign country, and that Mevacor® has been marketed in the US since 1987.

CONCLUSIONS & RECOMMENDATIONS

The proposed application is APPROVABLE (AE) pending resolution of the CMC issues listed in section H of this review. These comments should be forwarded to the applicant as an INFORMATION REQUEST (IR) letter.

Mike Adams
Review Chemist, HFD-820

Steve Moore
Chemistry Team Leader, HFD-820

cc:
NDA 21-316
HFD-510/div file
HFD-510/W.Koch/CSO
HFD-820/M.Adams/CMC/11-01-01
R/D Initial: S.Moore/11-19-01
Filename: c:\my documents\21316111.doc.1MA

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/s/

Mike Adams
11/27/01 01:18:46 PM
CHEMIST

Stephen Moore
11/27/01 05:45:58 PM
CHEMIST

APPEARS THIS WAY ON ORIGINAL

WITHHOLD 98 PAGE (S)