

Protocol 146-011

This was a 12-week extension study enrolling patients who completed Study 146-009 or Study 146-010. The study design was a randomized, double-blind study with patient assigned to treatment with daily doses of either 40 or 60 mg of ALTOCOR.

The patient population studied in all 3 clinical trials consisted of individuals with hypercholesterolemia defined as those with a fasting plasma LDL-C levels (off therapy) based on the presence of CHD, PVD, CVD, or other risk factors:

Table 1. LDL-C Selection Criteria for NDA 21-316

| Risk Category | LDL-C Level required for study entry |
|---|--------------------------------------|
| CHD, PVD, or CVD present | >100 mg/dL |
| CHD, PVD, or CVD absent but ≥ 2 RFs present | ≥130 mg/dL |
| CHD, PVD, or CVD absent but < 2 RFs present | ≥160 mg/dL |

EFFICACY RESULTS OF CLINICAL STUDIES

(Note: the term lova or lovastatin in this section refers to ALTOCOR and the term meva refers to MEVACOR)

Protocol 146-009

This was a 16-week, randomized, double-blind, placebo-controlled, dose-response study which included a 12-week treatment phase comparing placebo with lovastatin 10, 20, 40, and 60 mg. After screening of 287 individuals and a 4-week dietary placebo run-in period, a total of 172 patients were randomized to the 5 treatment groups as follows: placebo (n=34); lova 10 (n=35); 20 (n=34); 40 (n=33); or 60 mg (n=36). Baseline characteristics across all treatment groups (from ITT population) were similar as summarized in Table 17 of Dr. Pariser's review.

Twelve (7%) of the randomized population dropped out of the study with the most common reason being adverse event (3%) followed by consent withdrawal (2%) and other (2%). There were no drop-outs due to AEs at the highest dose of ALTOCOR.

The primary efficacy analysis was the percent change in LDL-C from baseline to endpoint in the ITT population (n=169). Secondary efficacy endpoints included percent change in total-C, HDL-C, and TGs from baseline to endpoint in this same population. Table 2 below summarizes the lipid changes for Protocol 146-009.

Table 2. Summary of Lipid Efficacy Results from Protocol 146-009 (from Dr. Pariser's Table 1)

| Treatment | Mean % Chg From Baseline to Endpoint | | | | |
|------------|--------------------------------------|-------|-------|-------|-------|
| | n | LDL-C | TC | HDL-C | TG |
| Placebo | 34 | 1.3 | 3.4 | +5.6 | 8.7 |
| Lova 10 mg | 33 | -23.8 | -17.9 | +9.4 | -17.3 |
| Lova 20 mg | 33 | -29.6 | -20.9 | +12.0 | -13.0 |
| Lova 40 mg | 33 | -35.8 | -25.4 | +13.1 | -9.9 |
| Lova 60 mg | 35 | -40.8 | -29.2 | +11.6 | -25.1 |

All the efficacy changes in the ALTOCOR treatment group were statistically significant from placebo changes with exception for the 10 mg dose effect on HDL-C.

ALTOCOR treatment resulted in a dose-related reduction in LDL-C and TC that was maximally achieved by 4 weeks and was sustained over the 16 weeks of treatment. In contrast, ALTOCOR treatment resulted in variable reductions in TGs and variable increases in HDL-C across all doses studied.

Protocol 146-010

This study was designed to compare the efficacy and safety of ALTOCOR to MEVACOR at two different daily doses: 20 and 60 mg. This study was designed to demonstrate a 3% greater LDL-lowering of ALTOCOR over MEVACOR. Total duration for this study was 34 weeks which included two 12-week active treatment periods separated by a 6-week washout period. After screening and a 4-week dietary, placebo run-in period, 358 patients were randomized to the following treatment sequences:

Table 3. Group Assignment and Treatment in Protocol 146-010

| Sequence | N | 12-wk Treatment Period 1 | 6-wk Washout Period | 12-wk Treatment Period 2 |
|-----------------------------|----|--------------------------|---------------------|--------------------------|
| Sequence A Lova20/Meva20 | 90 | Lovastatin 20 mg daily | Placebo | Mevacor 20 mg daily |
| Sequence B Meva20/Lova20 | 89 | Mevacor 20 mg daily | Placebo | Lovastatin 20 mg daily |
| Sequence C Lova60/Meva60 | 88 | Lovastatin 60 mg daily | Placebo | Mevacor 60 mg daily |
| Sequence D Meva60/Lova60 | 91 | Mevacor 60 mg daily | Placebo | Lovastatin 60 mg daily |

The baseline characteristics across all treatment groups were similar as summarized in Dr. Pariser's review.

Of the 358 randomized patients, 70 (20%) discontinued treatment prior to study completion for the following reasons: adverse events (8%); consent withdrawal (7%); other (3%); and protocol violation (2%). There did not appear to be a predominance of any one of these reasons in any treatment group.

The primary efficacy analysis was the percent change in LDL-C from baseline to endpoint with comparisons made between the ALTOCOR 20 versus MEVACOR 20 mg groups and between the ALTOCOR 60 versus MEVACOR 60 mg groups. Results from either the ALTOCOR or MEVACOR groups were pooled from Periods 1 and 2 active treatment. For example, the ALTOCOR 20 mg efficacy results included patients from treatment sequence A who received lovastatin 20 mg in the first active treatment period and patients from treatment sequence B who received lovastatin 20 mg in the second active treatment period (see Table 3 above). Baseline lipid values for Period 1 were averages of Study Visits 3 and 4 and baseline lipid values for Period 2 were averages of Study Visits 7A and 8. Study visits for Protocol 146-010 are summarized in Table 31 of Dr. Pariser's review.

The primary efficacy results are summarized below:

Table 4. Primary Efficacy Results for Protocol 146-010

| Treatment Group (n) | Baseline (SD) | Mean % Chg (SD) |
|---------------------|--------------------|-----------------|
| Lova 20 mg (n=149) | 183.3 mg/dL (35.5) | -26.3 |
| Meva 20 mg (n=146) | 179.1 mg/dL (37.3) | -23.1 |
| Lova 60 mg (n=146) | 177.6 mg/dL (31.6) | -34.7 |
| Meva 60 mg (n=147) | 178.6 mg/dL (33.4) | -33.0 |

Treatment with ALTOCOR at daily doses of 20 and 60 mg resulted in comparable LDL-lowering efficacy as Mevacor at similar doses. The ALTOCOR 20 mg results were significantly greater than the Mevacor 20 mg results whereas there was no statistical difference between the two treatment groups at the 60 mg dose.

The secondary efficacy analyses included the percent changes in total-C, HDL-C, and TG from baseline to endpoint in a similar pooling of results from Periods 1 and 2 active treatment. Table 5 summarizes the secondary efficacy results.

Table 5. Mean % Change (SD) at Endpoint in Protocol 146-010 for Secondary Efficacy Variables

| Treatment Group | Total-C | HDL-C | TGs |
|--------------------|---------|-------|-------|
| Lova 20 mg (n=149) | -19.0 | +3.7 | -8.3 |
| Meva 20 mg (n=146) | -17.1 | +3.9 | -11.1 |
| Lova 60 mg (n=147) | -26.0 | +5.0 | -17.5 |
| Meva 60 mg (n=147) | -25.1 | +5.2 | -18.6 |

Treatment with ALTOCOR at daily doses of 20 and 60 mg resulted in comparable changes in total-C, HDL-C, and TGs as treatment with Mevacor at similar doses.

The following figure, obtained from Ms. Joy Mele's statistical review, shows comparable LDL and Total-C lowering efficacy between ALTOCOR and MEVACOR at doses of 20 and 60 mg. This figure also shows that there is no carry-over effect from Period 1 and that LDL-levels returned to pre-treatment levels during the washout period.

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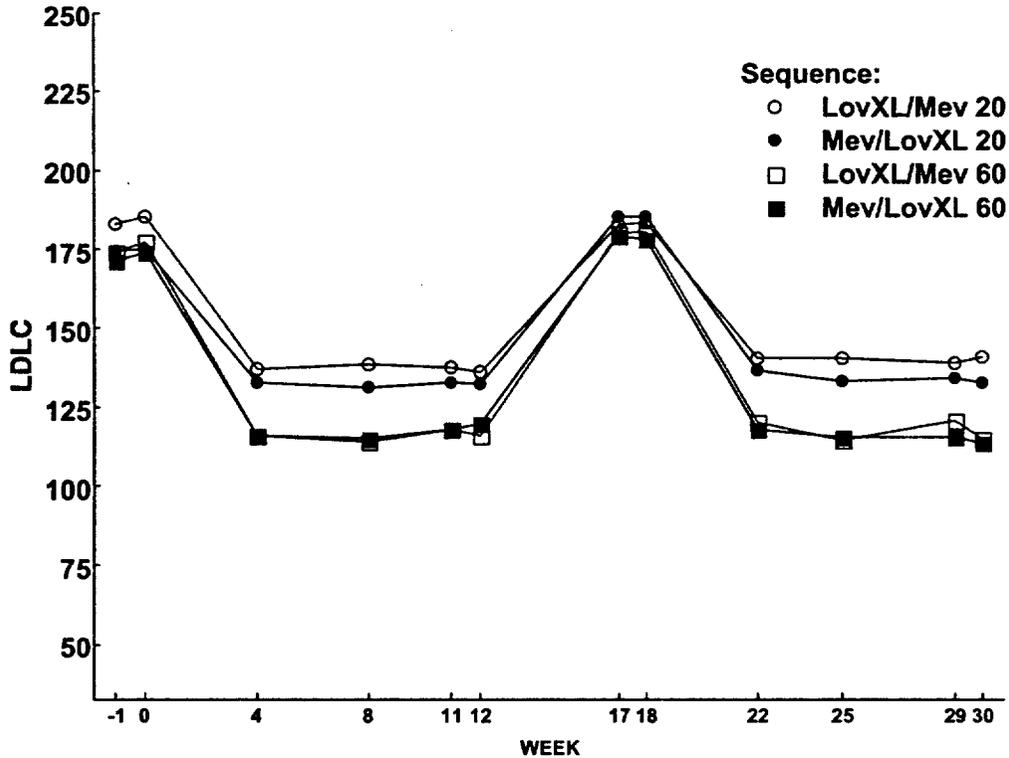
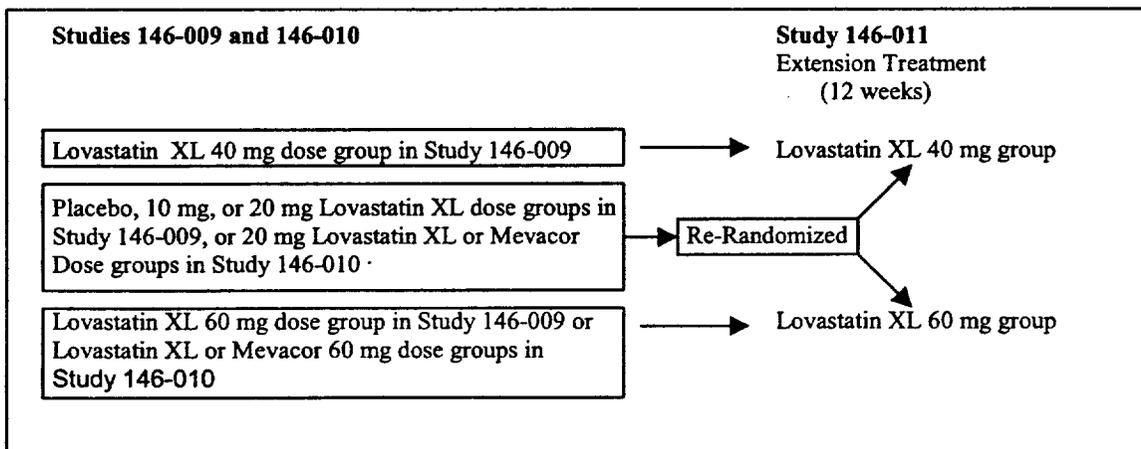


Figure 2. LDL-C Values in Protocol 146-010 (obtained from FDA statistical review by Joy Mele, MS)

Protocol 146-011

This study was a 12-week extension study of Protocols 146-090 and 146-010 wherein patients were treated with either lovastatin 40 mg or 60 mg once daily. Treatment assignments were determined as depicted in the following diagram obtained from Dr. Pariser's review:

Figure 3. Treatment Assignment for Protocol 146-011



There were 365 patients from 448 completing Protocols 146-090 or 146-010 who were enrolled in the extension study. Slightly more than half of these (54%) were re-randomized to receive either lovastatin 40 or 60 mg while 46% continued on their previous treatment for an additional 12 weeks. Efficacy analyses were performed on 356 patients (intent-to-treat population).

Twenty-five patients (6.8%) discontinued treatment prior to study completion for the following reasons: adverse event (4%); consent withdrawal (2%); and other (1%).

The primary efficacy analysis was the percent change in LDL-C from baseline to endpoint in the ITT population. Both the 40 and 60 mg treatment groups demonstrated statistically significant decreases in LDL-C from baseline although there was no difference between the two groups.

Table 6. Primary Efficacy Results for Protocol 146-011

| Treatment Group | n | Mean % Chg (SD) | p-value |
|-----------------|-----|-----------------|----------|
| Lova 40 mg | 124 | -33.3 (11.7) | p<0.0001 |
| Lova 60 mg | 232 | -33.7 (15.6) | p<0.0001 |

The secondary efficacy analyses included percent changes in total-C, HDL-C, and TG from baseline to endpoint in the same population. The following table summarizes these results.

Table 7. Mean % Chg (SD) in Secondary Efficacy Variables for Protocol 146-011

| Treatment Group | Total-C | HDL-C | TG |
|-----------------|--------------|-------------|--------------|
| Lova 40 mg | -24.6 (8.2) | +7.1 (14.0) | -14.2 (26.2) |
| Lova 60 mg | -24.8 (11.8) | +7.1(13.2) | -14.7 (30.8) |

All changes in secondary efficacy variables were statistically significant from baseline (p<0.0001) although similar to LDL-C, there were no differences between the 40 and 60 mg treatment groups.

Conclusions on Efficacy of ALTOCOR

The extended-release formulation of lovastatin at daily doses of 10, 20, 40, and 60 mg is effective in lowering total-C and LDL-C. This response to therapy is dose-related, achieved by 4-weeks, and sustained over the duration of treatment. ALTOCOR treatment does result in statistically significant changes TG and HDL-C; however, these changes are variable and are not dose-related based on the results of Protocol 146-090.

The sponsor's rationale that a extended-release formulation of lovastatin would provide for greater LDL-lowering efficacy than the immediate-release formulation was tested in Protocol 146-010. Although ALTOCOR 20 mg did achieve a statistically greater reduction in LDL-C and total-C compared to MEVACOR, this was not evident at the 60 mg dose. The results of Protocol 146-090 show comparable lipid-altering effects between ALTOCOR and MEVACOR.

The efficacy results of Protocol 146-011 demonstrate significant reductions in LDL-C, total-C, and TGs and increases in HDL-C with ALTOCOR daily doses of 40 and 60 mg.

Although these results show no difference between the two doses studied, the results of Protocol 146-090 unequivocally demonstrated a dose-response relationship for LDL and total-C lowering across all doses proposed by the sponsor including the 40 and 60 mg dose.

It is interesting to note that the LDL-lowering efficacy of ALTOCOR was quite variable across all three protocols (see Table 8).

Table 8. Mean % Reduction in LDL-C for all 3 Clinical Protocols

| | Lovastatin 20 mg | Lovastatin 40 mg | Lovastatin 60 mg |
|------------------|------------------|------------------|------------------|
| Protocol 146-090 | -29.6 | -35.8 | -40.8 |
| Protocol 146-010 | -26.3 | NA | -34.7 |
| Protocol 146-011 | NA | -33.3 | -33.7 |

This was explored in detail by Ms. Mele in her statistical review of the application who did not find any inconsistencies in the lipid-altering response between the two trials, Protocol 146-090 and 146-010, with exception for the TG-lowering response of the 20 mg doses (see Figure 9 from Ms. Mele's review).

SAFETY RESULTS OF CLINICAL STUDIES

The consideration for approval of ALTOCOR at daily doses of 10 to 60 mg may include the Agency's findings of safety and tolerability for lovastatin as established in data submitted for MEVACOR. The safety of MEVACOR up to 80 mg daily doses has been adequately studied in long-term placebo-controlled studies. The Expanded Clinical Evaluation of Lovastatin (EXCEL) study was a Phase 4 study comparing MEVACOR 10 to 80 mg to placebo for 48 weeks with a 2-year extension phase in over 8,000 patients. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAP/TexCAPS) was a 5-year placebo-controlled study involving 6,605 patients with approximately half of these patients exposed to MEVACOR 20 or 40 mg once daily. Overall, MEVACOR (lovastatin) is well-tolerated with the most serious safety concern being myopathy with rare deterioration to rhabdomyolysis. The incidence of this AE is approximately 0.08% for myopathy and 0.03% for rhabdomyolysis. This risk is increased with the concomitant use of certain medications (e.g., fibrates, niacin, cyclosporine, or 3A4 inhibitors). Another safety concern includes occasional increases in hepatic transaminases. The incidence of clinically relevant increases in ALT and AST defined as consecutive greater than 3x ULN is <1% in long-term placebo-controlled trials with no difference from placebo. Most of these laboratory abnormalities resolve spontaneously or with temporary interruption of treatment. Both of these safety concerns are discussed in the MEVACOR drug label and will be similarly applied to the ALTOCOR label as there is no evidence to expect any difference between these two products with respect to these rare adverse experiences.

In addition to the safety findings of MEVACOR, the clinical development program for ALTOCOR is sufficient to allow for labeling that is unique to this product. There were at least 588 patients exposed to ALTOCOR in the clinical studies submitted to this NDA (excluding single-dose pK studies). The patient exposures by treatment, dose and duration are summarized in the following table obtained from Dr. Pariser's review.

Table 9. Safety Exposures for NDA 21-316

| Study | Placebo | Treatment | | | | | | | | | Total |
|-----------------------------|-----------|---------------|------------|------------|------------|------------|------------|-----------|------------|------------|------------|
| | | Lovastatin XL | | | | | Mevacor | | | | |
| | | 10 mg | 20 mg | 40 mg | 60 mg | All | 20 mg | 40 mg | 60 mg | All | |
| Controlled Studies | | | | | | | | | | | |
| 146-009 | 34 | 35 | 34 | 33 | 36 | 138 | - | - | - | - | 172 |
| 146-010 | - | - | 162 | - | 167 | 329 | 166 | - | 163 | 329 | 358 |
| Total | 34 | 35 | 196 | 33 | 203 | 467 | 166 | - | 163 | 329 | 530 |
| Uncontrolled Studies | | | | | | | | | | | |
| 146-008 | - | - | - | 68 | - | 68 | - | - | - | - | 68 |
| 146-011* | - | - | - | 128 | 237 | 365 | - | - | - | - | 365 |
| Total | - | - | - | 196 | 237 | 433 | - | - | - | - | 433 |
| Phase II PK/PD Study | | | | | | | | | | | |
| 146-006 | - | - | - | 25 | - | 25 | - | 25 | - | 25 | 26 |
| Overall Total | 34 | 35 | 196 | 223 | 302 | 588 | 166 | 25 | 163 | 354 | 624 |

*majority of patients exposed to lovastatin XL in studies 146-009 and 146-010

#includes additional 28 patients previously exposed to placebo in study 146-009, exposed to lovastatin XL in 146-011

Although the above exposures are inadequate to detect the serious rare adverse effects such as rhabdomyolysis, they are sufficient for discussion on the relative safety of ALTOCOR to MEVACOR.

Discontinuations for AEs were 6%, 3%, and 4% for placebo, ALTOCOR, and MEVACOR groups, respectively, and the percentage of patients reporting any AE was identical in all 3 groups at 65%. No cases of myopathy, rhabdomyolysis or hepatitis were observed in this clinical development program. There was only one patient who experienced ALT or AST greater than 3x ULN. This patient was enrolled in the Lova20/Meva20 mg group of Protocol 146-010. Her ALT elevation of 567 IU/mL was considered due to choledocholithiasis, cholecystitis, and pancreatitis diagnosed 4 days after she was discontinued from therapy. The incidence of CPK > 10x ULN was < 1% with 2 patients in the ALTOCOR 20 mg group and 1 in the MEVACOR 20 mg group recorded with this event.

From the sponsor's pooled safety analysis (controlled and uncontrolled) and Dr. Pariser's review of the individual controlled studies, the safety profile of ALTOCOR is similar to that of MEVACOR's.

LABELING

The proposed labeling for ALTOCOR included efficacy and safety data for lovastatin immediate-release. Since the sponsor also conducted clinical studies with ALTOCOR, data specific to this product were also presented in the proposed label. The primary reviews from the medical, statistical, clinical pharmacology, chemistry, and pharmacology/toxicology disciplines have detailed discussions of the proposed label and the discipline-specific comments. This memo will highlight the major clinical/statistical proposals and issues in the proposed label.

Information obtained from studies using lovastatin immediate-release (MEVACOR) can be presented in the ALTOCOR label but such statements need to specify that the data are obtained from the immediate-release formulation. Information that is still under exclusivity protection cannot be presented in the label until after the exclusivity has expired. All safety information relevant to lovastatin immediate-release needs to be conveyed in the extended-release label as this application did not present data suggesting a better safety profile than MEVACOR.

The indications sought by the sponsor in this application include:

1. []
2. to slow the progression of coronary heart disease
3. as an adjunct to diet and other nonpharmacological measures to reduce elevated total-C, LDL-C, Apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia

Of these three, indication #1

[] this indication will not be included in the label approved with this current application. Indication #3 differs from the MEVACOR label in that ALTOCOR is indicated to lower ApoB and TG and increase HDL-C. The results of Protocol 146-090 support the conclusion that ALTOCOR therapy does lower TG and increase HDL-C but these responses are not dose-related. This information should be conveyed under the Clinical Studies subsection of the CLINICAL PHARMACOLOGY section describing the clinical trials with ALTOCOR. The inclusion of ApoB is acceptable despite the lack of such data from clinical studies submitted to this NDA since the published literature supports this lipoprotein to be strongly associated with LDL-C and clinical cardiovascular risk.

The variability in LDL-lowering efficacy of Protocol 146-090 should be conveyed in the label as proposed in the following figure from Ms. Mele's review.

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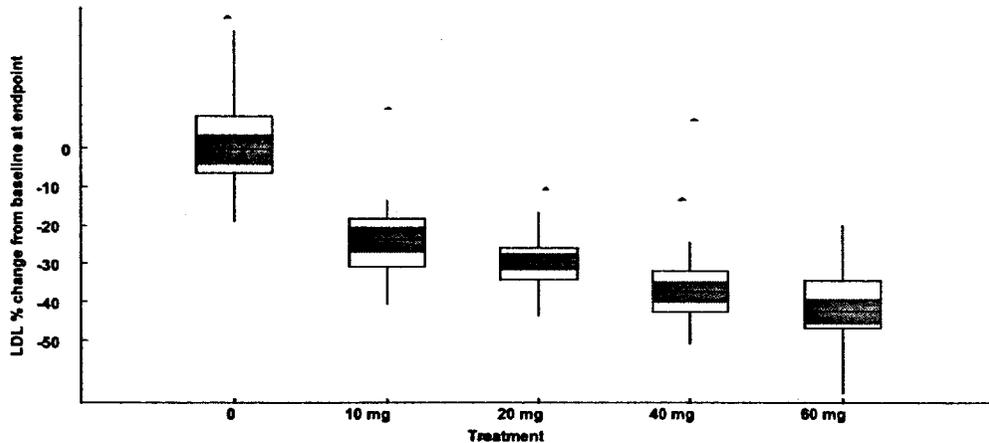


Figure 4. Study 146-009 Boxplots of LDL % change from baseline at Week 12 LOCF obtained from Joy Mele's Statistical Review

FINANCIAL DISCLOSURE

This information was submitted by the sponsor and reviewed by Dr. Pariser and found to be adequate.

PEDIATRIC STUDIES

The sponsor submitted an _____ study proposal _____. The Agency is unable to issue a Written Request for any pediatric study with ALTOCOR at present until the safety and effectiveness of the immediate-release formulation of lovastatin has been evaluated in this similar population.

CONCLUSIONS

Aura Laboratories has submitted a 505(b)(2) application for ALTOCOR (lovastatin extended-release) tablets at dosage strengths 10, 20, 40, and 60 mg once daily. The data supporting the approval of this product come from clinical studies conducted and submitted by the sponsor as well as reference to published literature and efficacy and safety data reviewed by the Agency for the listed product, MEVACOR.

The clinical studies reviewed in this application support the effectiveness of ALTOCOR 10-60 mg at lowering total-C and LDL-C in a dose-related fashion. Treatment with ALTOCOR also reduces TG and _____ levels although these response are variable and not dose-related. ALTOCOR was well-tolerated in the clinical studies with a similar safety and efficacy profile to MEVACOR evaluated at identical doses.

RECOMMENDATIONS

Pending labeling negotiations, this application should be approved for the following indications:

1. as an adjunct to diet for the reduction of elevated total-C, LDL-C, Apo B, and TG and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson types IIa and IIb)
2. to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower Total-C and LDL-C to target levels

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

recommendation code: AP

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/s/

Mary Parks
1/18/02 03:02:26 PM
MEDICAL OFFICER

David Orloff
1/30/02 10:49:05 AM
MEDICAL OFFICER
Concur with Dr. Parks. Start dose 10-60 mg. Application
approvable with CMC deficiencies. Ph 4 commitment for
biopharm study. 1-21-02 faxed labeling OK save for
CMC comments in letter. labeling not approvable
due to exclusivity.

**APPEARS THIS WAY
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Memo To File

NDA #: 21-316
Submission: Response to Approvable Letter, response dated 18-Feb-2002, AZ
Drug: Lovastatin extended-release
Sponsor: Aura Laboratories, Inc.
Reviewer: Anne R. Pariser, M.D., Medical Officer, DMEDP
Date: 17-Apr-2002

A review of the sponsor's Labeling and Clinical and Regulatory response to the Approvable Letter (dated 30-Jan-2002) was conducted, and the findings are as follows:

- 1) The Division's request for removal of references to _____ data from the label was performed by the sponsor and this reference does not appear in the revised label.
- 2) No new safety or efficacy data was submitted for review.

No other information for Medical/Clinical review was contained in the sponsor's response.

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/s/

Anne Pariser
4/17/02 11:08:23 AM
MEDICAL OFFICER

Mary Parks
4/18/02 12:14:29 PM
MEDICAL OFFICER

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Memo To File

NDA #: 21-316
Submission: N 000 SU, dated 08-Jan-2002
Drug: Lovastatin extended-release
Sponsor: Aura Laboratories, Inc.
Re: 8-Month Safety Update
Reviewer: Anne Pariser, M.D.
Date: 23-Jan-2002

The sponsor submitted an 8-Month Safety Update to NDA # 21-316 (N 000 SU, dated 08-Jan-2002). The cover letter noted that there have been no new additional safety data generated for this NDA since the 120-Day Update (120-Day Update reviewed as part of NDA application). In addition, there have been no additional clinical studies conducted under this NDA. No other information was contained in the submission.

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/s/

Anne Pariser
1/23/02 09:00:28 AM
MEDICAL OFFICER

Mary Parks
1/23/02 12:18:19 PM
MEDICAL OFFICER

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PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # : 21-316 Supplement Type (e.g. SE5): N Supplement Number:

Stamp Date: 3/30/01 Action Date: 6/26/02

HFD 510 Trade and generic names/dosage form: Altacor (lovastatin) Extended Release Tablets 10/20/40/60 mg

Applicant: Aura Laboratories, Inc. Therapeutic Class:

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1 Lowering total cholesterol, LDL-C and triglycerides and raising HDL-C, and slowing of the progression of atherosclerosis

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 10 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 10 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): 07/01/2004

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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this page is the manifestation of the electronic signature.**

/s/

William Koch
6/26/02 02:19:53 PM

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FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21316/000 Action Goal:
Stamp: 30-MAR-2001 District Goal: 01-DEC-2001
Regulatory Due: 30-JAN-2002 Brand Name: (LOVASTATIN)E-R
Applicant: AURA LABS 10/20/40/60MG TABS
401 HACKENSACK AVE 9TH FLOOR Estab. Name:
HACKENSACK, NJ 07601 Generic Name: LOVASTATIN EXTENDED RELEASE
Priority: 3S TABS
Org Code: 510 Dosage Form: (EXTENDED-RELEASE TABLET)
Strength: 10, 20, 40, 60 MG

Application Comment:

FDA Contacts: S. KELLY (HFD-510) 301-827-6394 , Review Chemist
S. MOORE (HFD-510) 301-827-6430 , Team Leader

Overall Recommendation: ACCEPTABLE on 29-JUN-2001 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 08-JUN-2001 by S. FERGUSON (HFD-324) 301-827-0062

Establishment: 1058844

ANDRX PHARMACEUTICALS INC
4001 SW 47TH AVE
FORT LAUDERDALE, FL 33314

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: TTR OAI Status: NONE

Estab. Comment: DRUG PRODUCT MANUFACTURER, FINAL DOSAGE FORM PACKAGER, FINAL
DOSAGE FORM, RELEASE TESTING AND STABILITY TESTING (on 23-APR-2001
by S. KELLY (HFD-510) 301-827-6394)

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|-------------------|-------------|-----------|------------|---|------------|
| SUBMITTED TO OC | 23-APR-2001 | | | | KELLYS |
| SUBMITTED TO DO | 24-APR-2001 | GMP | | | DAMBROGIOJ |
| DO RECOMMENDATION | 27-APR-2001 | | | ACCEPTABLE BASED ON FILE REVIEW | PFIGAROL |
| | | | | F/U GMP INSPECTION CONCLUDED 4/12/01 FOUND FIRM HAD MADE PROMISED CORRECTION. ALL PREVIOUS WITHHOLD RECOMMENDATIONS HAVE BEEN CHANGED TO ACCEPTABLE AND ALERTS HAVE BEEN REMOVED. | |
| OC RECOMMENDATION | 30-APR-2001 | | | ACCEPTABLE DISTRICT RECOMMENDATION | DAMBROGIOJ |

Establishment: []

DMF No: AADA:

Responsibilities: _____

Profile: CFN OAI Status: NONE

Estab. Comment: _____ LOVASTATIN (on 23-APR-2001 by S.
KELLY (HFD-510) 301-827-6394)

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|-------------------|-------------|-----------|------------|--------------------------------|---------|
| SUBMITTED TO OC | 23-APR-2001 | | | | KELLYS |
| OC RECOMMENDATION | 23-APR-2001 | | | ACCEPTABLE BASED ON PROFILE | EGASM |

Establishment: []

DMF No: AADA:

FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT

Responsibilities: _____
 Profile: CTL OAI Status: NONE
 Estab. Comment:

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|-------------------|-------------|-----------|------------|--------------------------------|-----------|
| SUBMITTED TO OC | 29-JUN-2001 | | | | KELLYS |
| OC RECOMMENDATION | 29-JUN-2001 | | | ACCEPTABLE BASED ON PROFILE | FERGUSONS |

Establishment: []

DMF No: AADA:
 Responsibilities: _____
 Profile: CTL OAI Status: NONE
 Estab. Comment: [(on 23-APR-2001 by S. KELLY (HFD-510) 301-827-6394)]

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|-------------------|-------------|-----------|------------|--------------------------------|------------|
| SUBMITTED TO OC | 23-APR-2001 | | | | KELLYS |
| OC RECOMMENDATION | 24-APR-2001 | | | ACCEPTABLE BASED ON PROFILE | DAMBROGIOJ |

Establishment: []

DMF No: AADA:
 Responsibilities: _____
 Profile: CTL OAI Status: NONE
 Estab. Comment: [(on 23-APR-2001 by S. KELLY (HFD-510) 301-827-6394)]

| Milestone Name | Date | Req. Type | Insp. Date | Decision & Reason | Creator |
|----------------------|-------------|-----------|-------------|---------------------------------------|------------|
| SUBMITTED TO OC | 23-APR-2001 | | | | KELLYS |
| SUBMITTED TO DO | 24-APR-2001 | GMP | | | DAMBROGIOJ |
| ASSIGNED INSPECTION | 02-MAY-2001 | PS | | | RBROWN4 |
| INSPECTION PERFORMED | 08-JUN-2001 | | 23-MAY-2001 | | NROLI |
| DO RECOMMENDATION | 08-JUN-2001 | | | ACCEPTABLE INSPECTION | NROLI |
| OC RECOMMENDATION | 08-JUN-2001 | | | ACCEPTABLE DISTRICT RECOMMENDATION | FERGUSONS |

APPEARS THIS WAY
 ON ORIGINAL

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)**

DATE RECEIVED: 03/20/02

DUE DATE: 04/19/02

ODS CONSULT #: 01-0148-1

TO: David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: William C. Koch
Project Manager
HFD-510

PRODUCT NAME:
Altacor
(Lovastatin Extended Release Tablet)
10 mg, 20 mg, 40 mg, and 60 mg

NDA SPONSOR: Aura Laboratories Inc.

NDA #: 21-316

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), the Division of Medication Errors and Technical Support (DMETS) conducted a re-review of the proposed proprietary name "Altacor" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION: DMETS does not recommend the use of the proposed name, Altacor. However, based on DMETS's concurrence with the Division, the sponsor should commit to submitting all potential and actual errors involving Altacor to the Office of Drug Safety. Furthermore, the sponsor should commit to changing the proprietary name, Altacor, if two or more reports of actual errors occur.

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 04/04/2002

NDA#: 21-316

NAME OF DRUG: **Altacor**
(Lovastatin Extended Release Tablet)
10 mg, 20 mg, 40 mg, and 60 mg

NDA HOLDER: Aura Laboratories Inc.

I. EXECUTIVE SUMMARY:

This consult was written in response to a March 20, 2002 request from the Division of Metabolic and Endocrine Drug Products (HFD-510) for a re-review of the proprietary name, Altacor.

DMETS conducted the initial review of the proprietary name Altacor on November 29, 2001 (ODS # 01-0148) and found the name acceptable. The Division re-submitted the proposed name for 90-day name review on March 20, 2002. During our final evaluation process of the proposed name, DMETS received a letter dated March 26, 2002 from _____ The letter expressed concerns that the approval of the proprietary name, Altacor, may cause medication errors with the recently approved _____ The portion of the letter is as follows (see Appendix I for the full letter):

J

On March 26, 2002, an expert panel discussion was conducted to re-evaluate the name, Altacor. The panel identified two additional proprietary names, Entocort EC and Atacand, that were thought to have the potential for confusion with Altacor. Furthermore, the panel expressed concern that the name, Altace, which was evaluated in ODS consult 01-0148, should be re-evaluated in light of our recent post-

marketing experiences. Upon re-review, DMETS found the name, Altacor, no longer acceptable due to the potential for confusion with Altace. Thereafter, the Division was notified of our decision via e-mail on April 2, 2002.

On April 4, 2002, the Division notified the sponsor, Andrx, of DMETS' concerns with the proposed name, Altacor. In response, the sponsor submitted a letter dated April 8, 2002 to the Division. According to the letter submitted by the sponsor, the name change is not warranted for the following reasons:

1. We surmise from the contents of the Approvable Letter, that the initial review by DDMAC (DMETS) raised no concern about confusion with other products.
2. An extensive evaluation for potential brand name confusion, conducted by the _____ showed little potential for confusion with Altace (or other products for that matter). The level of potential confusion appears to be well within acceptable parameters.
3. Altace is a capsule formulation while Altacor is a tablet formulation. Thus, if a prescription is properly written the word capsule/tablet distinguish the products.
4. The recommended dose range for the two products overlap only at 10 mg. We expect this to be a tiny percent of the market for Altacor based on current prescribing of Mevacor. Thus, very few prescriptions for Altacor will be written that could be confused with Altace.
5. A name change at this late date will impose a considerable hardship on Andrx, which is a small company with limited resources. Moreover, this could result in the use of a name that we have less time to evaluate for potential confusion, thus increasing the potential risk.

The firm also submitted a brief summary of _____ evaluation of the potential confusion between Altacor and Altace. According to the _____ study, "there was no evidence of meaningful confusion. In particular, none of the pharmacists who viewed a written prescription for Altacor confused it with Altace."

On April 8, 2002, a telephone conference was held between the Division and sponsor to discuss the Division and DMETS' concerns. Representatives from DMETS were also present during the telephone conference.

On April 9, 2002, the Division decided on the following actions:

1. The proposal by the sponsor to _____ from the market is not acceptable.
2. Prior to final action, the sponsor should commit to submitting all reports they receive of both potential and actual medication errors to the Office of Drug Safety. Potential errors are those instances in which there is a complaint/comment raised about the possibility of medication error. An actual error is one in which the wrong medication is dispensed, whether or not the patient takes the wrong medication, and whether or not he/she experiences an adverse reaction.
3. The sponsor should commit to changing the proprietary name of the product should there be two or more reports of medication error in which the patient actually received the wrong product (thus, instances of potential error do not count).

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound alike or look alike to Altocor to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Altocor. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Since the completion of our initial review of the proprietary name Altocor on November 29, 2001 (ODS # 01-0148), the Expert Panel identified two additional proprietary names, Entocort EC and Atacand, that were thought to have the potential for confusion with Altocor. Furthermore, the panel expressed concerns that the name, Altace, should be re-evaluated in light of our recent post-marketing experiences. These products are listed in table 1, along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

| Product Name | Dosage form(s), Established name | Usual adult dose* | Other** |
|--------------|--|--|---------|
| Altocor | Lovastatin Extended Release Tablet; 10 mg, 20 mg, 40 mg, and 60 mg | 10 mg to 60 mg QD at bedtime. | |
| Altace | Ramipril Capsule; 1.25 mg, 2.5 mg, 5 mg, and 10 mg | 2.5 mg to 20 mg QD. | SA/LA |
| Advicor | Niacin Extended Release and Lovastatin Tablet; 500 mg/20 mg, 750 mg/20 mg, and 1,000 mg/20 mg | 500 mg/20 mg to 1,000 mg/20 mg QD at bedtime. | SA/LA |
| Entocort EC | Budesonide Capsule; 3 mg | 9 mg QD in the morning for up to 8 weeks; may taper to 6 mg daily for 2 weeks prior to stopping. | SA/LA |
| Atacand | Candesartan Cilexetil Tablet; 4 mg, 8 mg, 16 mg, and 32 mg | 2 mg to 32 mg daily (may be given QD or BID). | SA/LA |

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. SAFETY EVALUATOR RISK ASSESSMENT

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

1. Look-Alike/Sound-Alike Names

In re-reviewing the proprietary name *Altacor*, the primary concerns raised were related to four sound-alike names that already exist in the U.S. marketplace, *Altace*, *Advicor*, *Atacand*, and *Entocort EC*.

DMETS initially reviewed the proposed name *Altacor* on November 29, 2001 (ODS # 01-148), and we found the name, *Altacor*, acceptable based on the information available from our databases at the time. However, our current post-marketing experience indicates that there is a potential risk of medication errors between the names that share the same prefix as "Alt" in *Altace* and *Altacor*. For instance, post-marketing experience with the drug products "Serzone" and "Seroquel" have demonstrated that having the same prefix may lead to medication errors. As of April 2, 2002, the Agency has received twenty-six (26) medication error reports involving Serozone and Seroquel from the Adverse Event Reporting System (AERS) database. Serzone and Seroquel share the same prefix, "Ser." Furthermore, they share the overlapping strengths (100 mg and 200 mg), dosage forms (tablets), and dosing interval (BID). Lastly, they are stored next to each other on pharmacy shelves, which is critical in causing unnecessary medication errors. Similarly, *Altacor* and *Altace* share the aforementioned commonalities. First, *Altacor* and *Altace* can look alike when scripted because they share the same prefix, "Alt" and similar endings "ce" and "cor" (see prescription below).

Altace
10mg
QD
#30

altacor
10mg
QD
#30

Second, both products share an overlapping route of administration (oral), strength (10 mg) and dosing interval (QD). Therefore, a prescription for "Altace 10 mg po QD" could be misinterpreted as "Altacor 10 mg po QD" or vice versa and lead to medication errors. In addition, *Altacor* will be placed in close proximity to *Altace* on pharmacy shelves, further increasing the risk of errors. We acknowledge that the two products have different dosage forms (tablet vs. capsule); however, different dosage form descriptions are either omitted from a prescription or overlooked by the pharmacist when scripted. If a patient inadvertently receives *Altacor* instead of *Altace*, he or she may remain untreated for hypertension and may also experience the side effects associated with the use of *Altacor* such as hepatotoxicity and myopathy. If a patient receives *Altace* instead of *Altacor*, a patient may experience headache, orthostatic hypotension, and dizziness. Furthermore, the patient's dyslipidemia would not be adequately treated and may lead to myocardial infarction, unstable angina, and coronary revascularization procedures.

DMETS reviewed the name, *Advicor*, in ODS consult 01-0148 and concluded that the potential confusion with *Altacor* is minimal. *Advicor*, which was approved by the Agency on December 17, 2001, contains the following active ingredients: niacin extended-release and lovastatin tablets. *Advicor* is indicated as an adjunct to diet for the reduction of _____

_____ On March 6, 2002, DMETS received a letter from _____ in which they expressed concerns that the approval of the proprietary name, *Altacor*, may cause medication errors _____ According to _____

However, there are differences between the two drug products that minimize the risk for error. *Advicor* will be available in 500 mg/20 mg, 750 mg/20 mg and 1000 mg/20 mg combination strength tablets. *Altacor*, on the other hand, will be available only in the following single strengths: 10 mg, 20 mg,

40 mg, and 60 mg. We believe that the difference in the strengths (combination vs. single) will help ensure that medication errors do not occur between the two products.

The Expert Panel identified Atacand as a potential look-alike/sound-alike name since our previous consult dated November 2001. Atacand, which is indicated for the treatment of hypertension, contains the active ingredient, candesartan. Atacand is available as 4 mg, 8 mg, 16 mg, and 32 mg tablets, and is dosed 2.5 mg to 32 mg daily, which can be given once or twice daily. Altocor and Atacand share an overlapping dosage form (tablet) and dosing interval (QD). Although, Altocor and Atacand do not share overlapping strengths, the strengths are numerically similar (4 mg vs. 40 mg, respectively). However, the proposed name Altocor does not look or sound very similar to Atacand; the prefixes "Alt" and "Ata" and suffixes "cor" and "cand" are not very similar when scripted or pronounced.

Entocort EC is another sound alike named identified by the panel since our consult dated November 2001. Entocort EC is indicated for the treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon and was approved by FDA on October 2, 2001. Although Entocort EC can look and sound similar to Altocor, the modifier, EC, clearly distinguishes one name from the other. In addition, both drugs are available in different strengths. Entocort EC is available as 3 mg tablets while Altocor will be supplied as 10 mg, 20 mg, 40 mg, and 60 mg tablets. The total daily dose also varies between the two drug products. Entocort EC is usually dosed 9 mg daily while Altocor is dosed from 10 mg to 60 mg daily at bedtime.

2. _____ Analysis

The sponsor, Andrx, requested _____ to evaluate the proposed proprietary name, Altocor. The _____ study cannot be accurately evaluated by DMETS due to a lack of important information. Such information include the details on the methodology of the study, the criteria for the selection of the participants, the demographics of the participants, the practice setting of each participant, how the participants were selected, how the prescriptions were distributed, how the prescriptions were given (eg. was the name given as part of a full prescription as in the real world?), and the environment of the study (eg. did it take place in a busy setting as in the real world?). The validation of the techniques was also not provided.

The _____ study included 40 internal medicine physicians, 10 cardiologists, and 50 pharmacists. The sample size used (100) in the study is quite small; not enough to detect all possible name confusions that might occur when the proprietary is put out in the real world. These study participants were asked to identify existing brand/generic drug names that sound and look like the proposed proprietary name, Altocor. The results submitted by the _____ demonstrated that 100 % of the pharmacists who viewed the "aided" written prescription for Altocor did not confuse it with Altace. In addition, none of the pharmacists who heard the "aided" prescription for Altocor confused it with Altace. However, for the "unaided" prescriptions for Altocor, the sound-alike and look-alike confusion among the study participants were 3 % and 1 %, respectively. Therefore, the _____ results support our findings in that the potential for confusion among Altocor and Altace does exist.

III. RECOMMENDATIONS:

DMETS does not recommend the use of the proposed name, Altocor. However, based on DMETS's concurrence with the Division, the sponsor should commit to submitting all potential and actual errors involving Altocor to the Office of Drug Safety. Furthermore, the sponsor should commit to changing the proprietary name, Altocor, if two or more reports of actual errors occur.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Hye-Joo Kim
4/19/02 08:38:05 AM
PHARMACIST

Alina Mahmud
4/19/02 08:40:45 AM
PHARMACIST

Carol Holquist
4/19/02 12:47:17 PM
PHARMACIST

Jerry Phillips
4/19/02 01:38:24 PM
DIRECTOR

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 06/27/01 **DUE DATE:** 11/30/01 **OPDRA CONSULT:** 01-0148

TO:

David Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH:

William C. Koch
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

PRODUCT NAME:

Altacor
(Lovastatin extended release tablet)
10 mg, 20 mg, 40 mg, 60 mg

MANUFACTURER:

Aura Laboratories Inc.

NDA #: 21-316

SAFETY EVALUATOR: Nora Roselle, Pharm.D.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), OPDRA conducted a review of the proposed proprietary name "Altacor" to determine the potential for confusion with approved proprietary and established names as well as pending names.

OPDRA RECOMMENDATION:

OPDRA has no objections to the use of the proprietary name "Altacor". This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document.

**APPEARS THIS WAY
ON ORIGINAL**

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3242
Fax: 301-480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 29, 2001
NDA NUMBER: 21-316
NAME OF DRUG: Altacor
(Lovastatin extended release tablets)
10 mg, 20 mg, 40 mg, 60 mg
NDA HOLDER: Aura Laboratories Inc.

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the tradename "Altacor", regarding potential name confusion with other proprietary/generic drug names. The firm originally submitted the tradename _____, but withdrew the name and is now submitting "Altacor" for their product. OPDRA has received word from the Division that there is discussion regarding a change in the name from extended release to _____
_____ We recommend that the Division consult Dan Boring (of the USAN council &LNC) for the proper designation of the established name.

PRODUCT INFORMATION

Altacor is the proposed proprietary name for lovastatin extended release tablets. Lovastatin is indicated for the treatment of dyslipidemia in patients who are at risk for atherosclerotic vascular disease. Lovastatin is a lactone that is hydrolyzed to B-hydroxyacid, a potent inhibitor of HMG-CoA reductase. HMG-CoA reductase is the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early step in the biosynthetic pathway for cholesterol. Altacor is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases, as well as during pregnancy and in nursing mothers. The recommended dosage is 40 mg or 60 mg once daily at bedtime. The recommended dosing range is 10-60 mg/day, in single doses. A starting dose of 10 or 20 mg may be considered for patients requiring smaller cholesterol value reductions. Altacor will be supplied in bottles of _____ 90 tablets in the following strengths: 10 mg, 20 mg, 40 mg, and 60 mg.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound alike or look alike to "Altacor" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS)⁴ was conducted.

The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Altacor". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Altacor. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have concerns about the name with regard to promotional claims.

Table 1

| Product Name | Dosage form(s), Generic name | Usual adult dose | Other |
|--------------|---|--|--------------------|
| Altacor | Lovastatin extended release tablet, 10 mg, 20 mg, 40 mg, 60 mg (bottles of 7, 30, 90) | 40-60 mg once daily at bedtime | |
| Altace | Ramipril, capsule 1.25 mg, 2.5 mg, 5 mg, 10 mg (bottles of 30, 100) | 2.5-5 mg once daily, up to 20 mg/day | L/A per OPDRA |
| Ala-Cort | Hydrocortisone 1 % cream (30 g, 90 g), topical lotion (118 mL) | Apply to affected areas as directed by physician | S/A, L/A per OPDRA |
| Inocor | Inamrinone lactate, injection 5 mg/mL (20 mL) | <u>I.V. Bolus:</u> 0.75 mg/kg over 2-3 min <u>Maintenance infusion:</u> 5-10 mcg/kg/min | L/A per OPDRA |
| Cetacort | Hydrocortisone 0.5%, 1% lotion (60 mL) | Apply to affected areas as directed by physician | L/A per OPDRA |
| Acticort 100 | Hydrocortisone 1% lotion (60 mL) | Apply to affected areas as directed by physician | S/A per OPDRA |

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

³ The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1>

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

| Product Name | Dosage form(s), Generic name | Usual adult dose | Other? |
|--------------|---|--|---------------------------------------|
| Altacor | Lovastatin extended release tablet, 10 mg, 20 mg, 40 mg, 60 mg (bottles of 30, 90) | 40-60 mg once daily at bedtime | |
| Dilacor XR | Diltiazem hydrochloride 180 mg, 240 mg (bottles of 30, 100) | 180-240 mg once daily maximum daily dose: 540 mg/day | S/A, L/A per OPDRA |
| Advicor | Niacin extended-release and lovastatin tablets, 500mg/20mg, 750mg/20 mg, 1000 mg/20 mg (bottles of 30, 180) | One 500 mg/20 mg tablet at bedtime | S/A, L/A per OPDRA |
| | | *Frequently used, not all-inclusive. | **L/A (look-alike), S/A (sound-alike) |

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

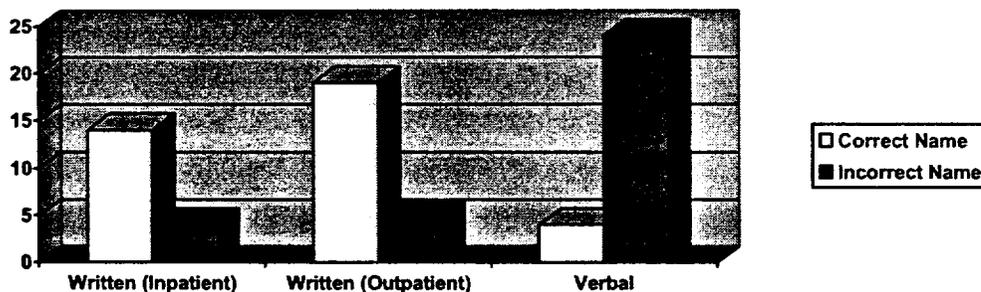
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Altacor with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 115 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and a prescription for Altacor (see below). These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

| HANDWRITTEN PRESCRIPTIONS | VERBAL PRESCRIPTIONS |
|---|--|
| <i>Inpatient:</i> Altacor 10 mg HS | <i>Outpatient:</i> Altacor 10 mg Take one tablet by mouth at bedtime Dispense #30 with no refills |
| <i>Outpatient:</i> Altacor 10 mg 1 po qhs # 30 | |

2. Results:

Results of these exercises are summarized below:

| Study | # of Participants | # of Responses (%) | Correctly Interpreted Altacor | Incorrectly Interpreted |
|--------------------|-------------------|--------------------|-------------------------------|-------------------------|
| Written: Inpatient | 38 | 18 (47%) | 14 (78%) | 4 (22%) |
| Outpatient | 39 | 24 (62%) | 19 (79%) | 5 (21%) |
| Verbal: Outpatient | 38 | 28 (74%) | 4 (14%) | 24 (86%) |
| Total | 115 | 70 (61%) | 37 (53%) | 33 (47%) |



Among the verbal outpatient Altacor prescriptions, 24 of 28 (86%) of the respondents interpreted the name **incorrectly**. Many of the incorrect name interpretations were phonetic, misspelled variations of "Altacor". Interpretations included Altacor, Alticort, Alticore, Altecourt, Atlacor, Altecor, Atacor, Alticon, Alticor, Alteco, and Aticor.

When examining the interpretations from the written inpatient and outpatient prescriptions, 33 of 42 (42%) of the respondents interpreted the name **correctly**. Again, many of the incorrect interpretations included misspelled, phonetic variations of the proposed name, Altacor. Responses included: Altocar, Altoca, Altocon, Altacar, and Altacor.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Altacor", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Altacor were Altace, Ala-Cort, and Inacor. Through further evaluation the following names were also believed to be of concern: Cetacort, Acticort, and Dilacor XR. Advicor, an NDA that is currently unapproved and unmarketed in the United States, was also found to have potential for name confusion with Altacor.

The potential for name confusion between the proposed name, Altacor, and the currently marketed product, Altace, is possible because they share some similarities. First, these names can look alike when scripted because they share common combinations of consonants and vowels. Second, both products share an overlapping strength (10 mg) and dosing interval (once daily). Lastly, both drugs have an oral route of administration. However, the proposed product, Altacor, and Altace have different indications for use. Altace, an angiotensin-converting enzyme inhibitor, is used in the treatment of hypertension while Altacor is indicated in the treatment of dyslipidemia. Altace is available as 1.25 mg, 2.5 mg, 5 mg, and 10 mg oral capsules. While Altacor will be available as 10 mg, 20 mg, 40 mg, and 60 mg tablets. Even though the two products contain overlapping strengths, Altace has a usual daily dose of 2.5 or 5 mg and Altacor is most often dosed as 40 or 60 mg daily. Likewise, each product has a once daily dosing interval, but Altacor is to be administered once daily at bedtime and Altace can be administered anytime throughout the day. In addition, the two products have different dosage forms (tablet vs. capsule). Thus, the risk of a product mix-up between Altace and Altacor is minimal.

Altace *Altacor*

Ala-Cort is a 1% topical corticosteroid used to help relieve the redness, swelling, itching, and discomfort of many skin problems. Ala-Cort is available in a cream and lotion formulation. Altacor is a cholesterol-lowering agent available in tablet formulation. Although Ala-Cort has look-alike and sound-alike qualities with Altacor, the two products belong to different pharmacologic classes and are available in different dosage forms. Moreover, the two products have different directions for use, routes of administration, strengths, and supply quantities. Therefore, the potential risk of confusing Ala-Cort with Altacor is low.

Alacort

Altacor

Inocor is an injectable dosage form of inamrinone, a phosphodiesterase inhibitor with positive inotropic and vasodilator activity. Inocor is used intravenously for the short-term treatment of severe, acute congestive heart failure that is unresponsive to other forms of therapy. The name Inocor can look similar to Altacor when scripted. However, Inocor is available as an injectable dosage form, while Altacor will be available in tablet form. The two drugs have different routes of administration, strengths, dosing intervals, and are not likely to be stored in close proximity due to the difference in formulation. Another significant difference between the two products is that Inocor must be dosed by body weight. The recommended starting dose of Inocor is a 0.75 mg/kg intravenous bolus given over 2 to 3 minutes, followed by a maintenance infusion of 5 to 10 mcg/kg/min. The risk of a product mix-up due to name confusion between Inocor and Altacor appears to be minimal.

Inocor

Altacor

Cetacort is a topical corticosteroid used to help relieve the redness, swelling, itching, and discomfort of many skin problems. Cetacort is available as a 0.5% and 1% lotion formulation. Although Cetacort can look like Altacor when scripted, the two products belong to different pharmacologic classes and are available in different dosage formulations. In addition, the two products will be available in different packaging, and may be stored in different areas of the pharmacy. Likewise, Cetacort and Altacor have different strengths, routes of administration, and directions for use. The potential risk of confusing Cetacort with Altacor is low.

Cetacort

Altacor

Acticort 100 is a topical corticosteroid used to help relieve redness, swelling, itching, and discomfort of many skin problems. Acticort is available as a 1% hydrocortisone lotion. The name Acticort sounds similar to Altacor. According to the Saegis¹ database, _____
_____ Acticort and Altacor differ in strength, dosage form, route of administration, supply quantity, and indication. The potential risk of name confusion between Acticort and Altacor appears to be minimal.

Dilacor XR, diltiazem hydrochloride, is a calcium channel blocking agent. Dilacor XR is effective in the treatment of angina pectoris due to coronary artery spasm, chronic stable angina pectoris, and hypertension. Although Dilacor XR can sound and look similar to Altacor when

¹ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

increased in size so that they are the most prominent information on the label.

2. The strengths on each container label should be prominent and clearly differentiated from the multiple strengths by using a contrasting color, boxing, or some other means.
3. We recommend that the container label state "PHYSICIAN SAMPLE – NOT TO BE SOLD".

PRESCRIPTION LABELING:

A. CONTAINER LABELS: (10 mg, 20 mg, 40 mg, 60 mg – _____ 90 tablets)

1. Regarding the container labels for the _____ tablet bottles, the net quantity statement should appear away from the product strength.
2. Drugs packaged in "unit of use" bottles and dispensed on an outpatient basis, such as the _____ 90 tablet bottles, should include Child Resistant Closures (CRC).
3. As per the container labels provided for the 90 tablet bottles, it is unclear whether the container labels are true to size. If the provided container labels are true to size, the proprietary and established names should be increased in size so that they are the most prominent information on the label.
4. The strengths on each container label for the 90 tablet bottles should be prominent and clearly differentiated from the multiple strengths to be provided by using a contrasting color, boxing, or some other means.

**APPEARS THIS WAY
ON ORIGINAL**

IV. RECOMMENDATIONS:

OPDRA has no objections to the use of the proprietary name Altocor.

This is considered a tentative decision and the firm should be notified that this name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

OPDRA recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

We recommend consulting Dan Boring (of the USAN council & LNC) for the proper designation of the established name.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam at 301-827-3242.

Nora Roselle, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

**APPEARS THIS WAY
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Nora L. Roselle
11/29/01 10:52:40 AM
CSO

Jerry Phillips
11/29/01 12:42:00 PM
DIRECTOR

Martin Himmel
11/29/01 03:34:14 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**



Koehn

Food and Drug Administration
Rockville MD 20857

NOV - 1 2001

Edward Gillie, M.D.
12751 New Brittany Blvd., Suite 501
Ft. Myers, Florida 33907

Dear Dr. Gillie:

Between September 17 and 19, 2001, Mr. Paul L. Figarole Jr., representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # 146-009) of the investigational drug, Lovastatin XL (———), performed for Aura Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects

We appreciate the cooperation shown Investigator Figarole during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/s/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

**APPEARS THIS WAY
ON ORIGINAL**



Koch

NOV - 1 2001

Margaret Drehobl, M.D.
15025 Innovation Drive, Suite 2E
San Diego, California 92128

Dear Dr. Drehobl:

Between August 20 and 30, 2001, Mr. Thomas Beilke, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # 146-009) of the investigational drug, Lovastatin XL, performed for Aura Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that there were no significant departures from federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects

We appreciate the cooperation shown Investigator Beilke during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/s/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

**APPEARS THIS WAY
ON ORIGINAL**



Koch

NOV - 1 2001

Food and Drug Administration
Rockville MD 20857

Jon A. LeLevier, M.D.
2067 W. Vista Way, Suite 270
Vista, California 92082

Dear Dr. LeLevier:

Between September 10 and 21, 2001, Mr. Thomas Beilke, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # 146-010) of the investigational drug, Lovastatin XL ———, performed for Aura Laboratories, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that there were no significant departures from federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Beilke during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/s/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

**APPEARS THIS WAY
ON ORIGINAL**