CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-316

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-316	Brand Name	Altocor
OCPB Division (I, II, III)	DPE-II	Generic Name	Lovastatin Extended Release Tablets
Medical Division	DMEDP	Drug Class	Lipid altering agents
OCPB Reviewer	Sang M. Chung, Ph.D.	Indication(s)	Cholesterol-lowering
OCPB Team Leader	Hae-Young Ahn, Ph.D.	Dosage Form	Tablet
		Dosing Regimen	Q.D.
Date of Submission	30-March-2001	Route of Administration	Oral
Estimated Due Date of OCPB Review	15-December-2001	Sponsor	Aura Laboratories, Inc.
PDUFA Due Date	30-January-2002	Priority Classification	S
Division Due Date	15-December-2001		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	8	8	
multiple dose:				
Patients-				
single dose:				
multiple dose:		1	1	
Dose proportionality -				
fasting / non-fasting single dose:	X	2	2	
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1	1	
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1	1	
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				

II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X			
solution as reference:				
alternate formulation as reference:	X			
Bioequivalence studies -	X	1	1	
traditional design; single / multi dose:	X			
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		9	9	

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Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-316
Brand Name:	Altocor™ Tablets
Generic Name:	Lovastatin modified-release tablets
Strength(s):	10, 20, 40, 60 mg
Sponsor:	Aura Laboratories, Inc. 401 Hackensack Ave. Hackensack, NJ 07601
Submission Date:	30-March-2001
Submission Type:	Original Application – Immediate release to Modified release
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Hae-Young Ahn, Ph.D.

I. Executive Summary

The sponsor has submitted original NDA 21-316 for Altocor™ as a cholesterol-lowering agent. It is the first lovastatin modified release (MR) formulation. Lovastatin release is controlled through the use of an ——— (enteric-coated).

According to the sponsor, the controlled-release statin formulation has been developed because the same total milligram dose of lovastatin is significantly more effective when administered twice-daily, than once-daily in EXCEL trial of Mevacor® (the reference immediate release formulation) and in some publications. In addition, the generally recommended starting dose of Altocor will be higher than that of Mevacor®.

The proposed dosing range of Altocor™ is 10-60 mg/day, in single doses. The proposed starting dose is 40 mg or 60 mg once a day given in the evening at bedtime. According to Mevacor® label, the usual recommended starting dose is 20 mg once a day given with the evening meal and the recommended dosing range is 10-80 mg/day in single or two divided doses; the maximum recommended dose is 80 mg/day.

The sponsor generated pre-clinical, clinical, and manufacturing data in the new formulation. Nine human studies were conducted to elucidate clinical pharmacology and biopharmaceutics of Altocor™. Relative bioavailability (BA) compared to Mevacor® was assessed in fed and fasting conditions for single-dose of 40-mg in healthy subjects. Also, BA was evaluated in hypercholesterolemia patients after multiple daily doses. Other studies were to estimate food effect, dose proportionality, and dosage form equivalence. Two studies about alternative formulations were not reviewed because the sponsor did not claim any information but those were included only as additional information.

The MR characteristics of Altocor™ was generally demonstrated with significantly longer T_{max} and lower C_{max} compared to those of Mevacor® after single-dose and multiple daily doses administration. Exposures as AUC and C_{min} were significantly higher in Altocor™ 40 mg than

Mevacor® 40 mg after multiple daily doses but there was no further safety concern according to the reviewing medical reviewer. Food reduced up to 54% lovastatin bioavailability of Altocor as reference of overnight fasting condition.

I-A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB/DPE-II) has reviewed NDA21-316 (Altocor™) submitted on 30-March-2001. The submission is acceptable to OCPB/DPE-II with proper reflection of comments. The Recommendation, Reviewers Comments, and Labeling Comments should be sent to the sponsor as appropriate.

I-B. Phase IV Commitment

The sponsor should develop a dissolution method and specification to assure both delayed and extended characteristics of the formulation. The sponsor can refer Guidance for Industry (SUPAC-MR: Modified release solid oral dosage forms).

/S/ 20-DEC-2001

Sang M. Chung, Ph.D. Date
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Final version signed by Team Leader

/S/ 20-DEC-2001

Hae-Young Ahn, Ph.D. Date

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II. Table of Contents

List of Tables

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III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor developed lovastatin modified release tablets and lovastatin release would be controlled through [redacted] Tablet core contains the active drug substance [redacted]

The sponsor attempted to assess dose proportionality within 10, 20, 40, and 60 mg Altocor. The correlation was based on doses versus dose normalized C_{max} and AUC (i.e., $NC_{max}=C_{max}$/Dose and NAUC=AUC/Dose) or doses versus body weight and dose normalized C_{max} and AUC (i.e., $NC_{max}=C_{max}$/Dose/BW and NAUC=AUC/Dose/BW).

It is recommended for the future studies to use power model between doses and AUCs. Also sameness test of clearance from each strengths, which is dose-normalized parameter, would be acceptable as an alternative. Upon reanalysis of the data using dose normalized AUC for dose linearity, results appear to show dose linearity between 10-60 mg of Altocor.

According to the sponsor's clinical trial data, mean % LDL-C change from baseline after 12 weeks were –23.8%, -29.6%, -35.8%, and –40.8 for 10mg, 20mg, 40mg, and 60mg Altocor.

Relative bioavailability of Altocor was assessed in 2 single dose studies compared to Mevacor, the reference immediate release tablet in healthy subjects. Delayed release characteristics was demonstrated in the study compared to Mevacor with significantly longer T_{max} and lower C_{max}. Bioavailability of lovastatin was increased by 41 to 51% compared to Mevacor under the fed and fasting conditions. The corresponding values were 14 to 33% for lovastatin acid. Proposed dosing frequency is once a day and it is the same as the immediate release of Mevacor. Efficacy and safety with Altocor was comparable to those of Mevocor according to the reviewing clinical reviewer. Pharmacokinetic parameters are summarized in Table I.

Table I Summary of pharmacokinetic parameters after single dose

		AUC (ng hr/ml)		C_{max} (ng/ml)		T_{max} (hr)	
		Altocor	Mevacor	Altocor	Mevacor	Altocor	Mevacor
under fed (AUC_{0-24hr})	Lovastatin	33.9±11.8	26.6±17.0	3.15±1.24	6.13±2.56	15.5±5.1	2.1±0.6
	Lovastatin acid	47.5±18.9	42.2±20.3	4.64±1.89	6.45±4.09	13.8±3.8	3.9±1.0
under fasting (AUC_{0-48hr})	Lovastatin	54.2±20.4	37.6±17.5	3.39±1.39	2.80±1.15	10.4±7.8	5.1±2.2
	Lovastatin acid	58.0±20.0	44.4±17.2	3.37±1.91	3.75±1.81	11.2±5.1	5.6±2.5

It was found that there is significant contribution of AUC_{24-48} to total AUC for Altocor. AUC_{24-48} compared to AUC_{0-48} is 37% and 34% for lovastatin and lovastatin acid, respectively, in the overnight fasting condition. Therefore, it is recommended to collect blood samples up to at least 48 hours after Altocor administration as PK characterization in the future studies.

Pharmacokinetic characteristics after multiple daily doses were within the prediction from single dose pharmacokinetics in hypercholesterolemia patients. Relative BA in patients was increased about 40% compared to Mevacor based on cross study comparison with Study 007 (before bedtime) and the results are compatible with that in healthy subjects. Also, other pharmacokinetic characteristics in patients are similar to those in healthy subjects.

Table II Summary of pharmacokinetic parameters after multiple daily doses

		$AUC_{0\text{-}24hr}$ (ng hr/ml)		C_{max} (ng/ml)		C_{min} (ng/ml)	
		Altocor	Mevacor	Altocor	Mevacor	Altocor	Mevacor
Day 1	Lovastatin	49.9±23.5	33.7±21.6	4.0±2.0	6.7±4.0		
	Lovastatin acid	38.6±31.4	84.1±63.1	2.9±2.5	11.7±6.9		
Day 28	Lovastatin	76.6±36.9	44.7±46.2	5.5±2.5	7.8±8.1	2.6±1.6	0.4±0.4
	Lovastatin acid	87.1±67.2	82.5±60.3	5.8±4.8	11.9±10.2	3.1±2.5	0.7±0.6

Exposure as $AUC_{0\text{-}24hr}$ at Day 28 after Altocor administration was significantly higher than Mevacor (ratio of 1.91). However, there was minimal efficacy difference between treatments as %LDL-C lowering from baseline (-42.48 and -38.86 for Altocor and Mevacor, respectively at Week 4). Factor to explain the result is not known.

The means of C_{min} were 6-fold and 5-fold higher for lovastatin and lovastatin acid, respectively, in Altocor treatment than those of Mevacor though there was no significant safety concern in this study according to the clinical reviewer. Distribution of C_{24hr} at Day 28 as trough concentration was shown in the following figure.

Lovastatin Lovastatin acid

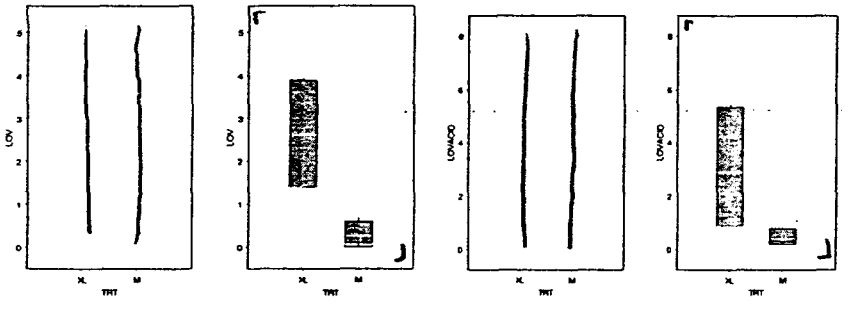

Figure 1 Distribution of C_{24hr} after Altocor or Mevacor multiple daily doses

The sponsor included chemical assay as well as enzyme assay that represented total and active inhibitor activity using HMG-CoA reductase in the multiple daily doses study. The results from the enzyme assay were different from chemical assay in accumulation ratio and relative bioavailability as reference of Mevacor (Table).

The enzyme assay is essentially based on mevalonic acid as a surrogate marker. However, it has not been clearly demonstrated up to now the scientific and regulatory validation of mevalonic acid as a biomarker.

Table III Geometric mean C_{max} and $AUC_{0\text{-}24hr}$ ratios (ALTOCOR/MEVACOR)

	C_{max} Ratio		$AUC_{0\text{-}24hr}$ Ratio	
	Day 1	Day 28	Day 1	Day 28
Lovastatin	0.62	0.84	1.49	1.91
Lovastatin acid	0.23	0.43	0.46	0.86
Total inhibitors of HMG-CoA reductase	0.29	0.48	0.56	0.96
Active inhibitors of HMG-CoA reductase	0.25	0.47	0.46	0.84

Food significantly reduced bioavailability of Altocor. Bioavailability after breakfast was 60% as reference under overnight fasting condition. Comparison across studies indicates that relative bioavailability of Altocor showed relationship with mealtime. The values of $AUC_{0\text{-}24hr}$ (ng hr/ml) were 42.75 administration of bedtime (about 10 PM) and 33.9 for administration immediately after dinner.

The following dissolution method and specification was proposed by the sponsor:
USP apparatus 2 (paddle) at 50 rpm, medium (900 mL) of — sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5 and temperature 37°C.

Table IV The proposed specification

Time (hr)	Amount Dissolved (%)
—	—
2	—
8	—
16	—

NMT: Not more than
NLT: Not less than

The sponsor claimed that Altocor has delayed as well as extended release characteristics. However, the proposed dissolution method and specification does not assure quality of delayed release for Altocor. Therefore, it is recommended that the sponsor establish new dissolution method and specification accordingly to assure both delayed and extended characteristics of the formulation. According to Guidance for Industry (SUPAC-MR: Modified release solid oral dosage forms), the following dissolution method for delayed release is recommended:

Dissolution should be tested in an acidic stage (i.e., 0.1 N HCl) for 2 hours followed by testing in the proposed dissolution condition for extended release.

Dissolution profiles of 60 mg Altocor were compatible between — , sodium lauryl sulfate concentration in the pH 6.5 medium. Minimum — concentration is currently recommended in the dissolution medium as long as solubility is not a limiting factor in the study. Therefore, — , sodium lauryl sulfate is recommended in the dissolution medium for extended release.

The following specification is recommended as an interim basis until the new dissolution method and specification established for quality control:

Time (hr)	Amount Dissolved (%)
2	—
8	—
—	—

Analytical procedures — were acceptable with proper —

III-A. Reviewers Comments

- The sponsor's proposed dissolution method and specification does not assure the quality of delayed release characteristics of Altocor. Therefore, it is recommended that the sponsor develop new dissolution method and specification accordingly to assure both delayed and extended characteristics of the formulation. The Agency's Guidance for Industry (SUPAC-MR: Modified release solid oral dosage forms) recommend the following dissolution method:

  Dissolution should be tested in an acidic stage (i.e., 0.1 N HCl) for 2 hours followed by testing in the proposed dissolution condition for extended release.

- The following dissolution method and specification is recommended as an interim basis:

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

  Dissolution specification;

Time (hr)	Amount Dissolved (%)
2	—
8	—
—	—

- For future studies, it is recommended that the sponsor characterize pharmacokinetics using plasma concentration profiles at least in 0-48 hours time period for Altocor because the contribution of $AUC_{24\text{-}48hr}$ to total AUC is significant.

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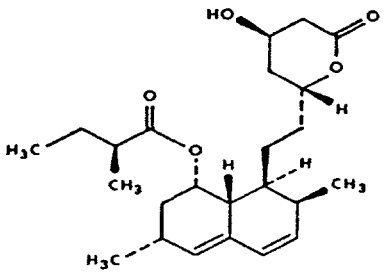
IV. Question Based Review

IV-A General Attributes

- **What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product ?**

Lovastatin was isolated from a fungus and is hydrolyzed to (beta)-hydroxyacid form (lovastatin acid) in the body. Lovastatin acid is an active metabolite of lovastatin and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the conversion of HMG-CoA to mevalonate as a rate limiting step in the biosynthesis of cholesterol.

Chemical structure of lovastatin is:



Lovastatin is insoluble in water (0.4 µg/ml according to the original NDA for Mevacor).

The MR tablet is composed of [redacted] and [redacted] coatings as shown in Figure 2. The coatings are [redacted] enteric coating, and seal coating [redacted] Tablet core contains the active drug substance, [redacted]

Figure 2 Schematic summary of Altocor coatings and core tablet

According to the reviewing chemistry reviewer, [redacted] enteric coating and seal coating [redacted]

The detailed compositions of formulations used in studies are summarized in Table V. The 10 mg and 20 mg tablets are qualitatively and quantitatively similar in its active and inactive ingredient except in the amount of lovastatin ——— The 20 mg and 40 mg tablets are proportionally similar but quantitatively different in the amounts of ——— The 40 mg and 60 mg are qualitatively and quantitatively similar except in the amounts of lovastatin ——— The 10 mg and 20 mg tablets have the same total tablet weight, and so do the 40 mg and 60 mg tablets.

Table V Composition of Altocor tablet

Unit Dose Composition of Lovastatin XL Tablets (mg)

Components	Tablet Strength (mg/tablet)			
	10 mg	20 mg	40 mg	60 mg
Lovastatin, USP ———	10.00	20.00	40.00	
——— Lactose, NF				
Polyethylene Oxide, NF ———				
Sodium Lauryl Sulfate, NF				
Butylated Hydroxyanisole, NF				
Polyethylene Oxide, NF ———				
——— Silicon Dioxide, NF				
Glyceryl Monostearate, NF				
———				
Sodium Chloride, USP ———				
Hydroxypropyl Methylcellulose ———				
———				
Talc, USP				

Components	Tablet Strength (mg/tablet)			
	10 mg	20 mg	40 mg	60 mg
Acetyltributyl Citrate, ———				
Sugar, Confectioner's ———				
Cellulose Acetate, ———				
Methacrylic Acid Copolymer, NF, Type B ———				
Triacetin, USP				
Polyethylene Glycol 400, NF				
———				
Candelilla wax ———				
———				
———				
———				
———				
Total	169.56	169.56	337.06	333.58

IV-B General Clinical Pharmacology

- **Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters ?**

Lovastatin and lovastatin acid, an active metabolite, were appropriately measured in plasma using ——— In addition, the sponsor included results of an enzyme assay to estimate total and active HMG-CoA inhibitor concentrations in plasma. Detailed description of the analytical procedures is summarized in the Section IV-D (Analytical Section).

- **Is dose proportionality of Altocor established ?**

The sponsor characterized dose proportionality in phase I studies (Study 146-007, 146-012). One was a single-dose pharmacokinetic study of Altocor 10, 20, and 40 mg in healthy male subjects (N=9, Study 007). The other study was a dose proportionality study in the dosage levels of 20, 40 and 60 mg after single oral dose to healthy subjects (N=24, 12 males, 12 females, Study 012).

Both studies were single-center, single-dose, open-label, randomized, three-period crossover design. All participants were served dinner at approximately 5:30 pm followed by dosing at approximately 10:00 pm, one-half hour before bedtime.

In the first study, Altocor was administered as one 10-mg, one 20-mg, and one 40-mg tablet. The sponsor attempted to establish dose linearity based on doses versus dose normalized C_{max} and AUC (i.e., $NC_{max}=C_{max}$/Dose and NAUC=AUC/Dose) as summarized in the following table. Dose proportionality was claimed between doses with no significant differences between dose-normalized parameters at alpha=0.05.

Table VI Summary of pharmacokinetic parameters in dose proportionality study 1

Lovastatin

Parameter	10 mg	20 mg	40 mg
NC_{max} (ng/ml)	0.10 ± 0.04	0.10 ± 0.03	0.10 ± 0.08
NAUC (ng-hr/ml)	1.45 ± 0.77	1.67 ± 0.67	1.39 ± 0.91

Lovastatin Acid

Parameter	10 mg	20 mg	40 mg
NC_{max} (ng/ml)	0.11 ± 0.10	0.11 ± 0.07	0.10 ± 0.07
NAUC (ng-hr/ml)	1.90 ± 1.52	1.89 ± 1.26	1.83 ± 1.58

In the second study, Altocor was administered as one 20-mg, one 40-mg, and 60 mg as co-administration of one 20-mg and one 40-mg formulation. The sponsor claimed dose proportionality between doses of 20, 40, 60 mg with body weight and dose normalized C_{max} and AUC (i.e., $NC_{max}=C_{max}$/Dose/BW and NAUC=AUC/Dose/BW). Also, linearity was claimed with regression analysis between doses and the normalized parameters as summarized in the following tables and figures.

Table VII Summary of pharmacokinetic parameters in dose proportionality study 2

Lovastatin

Parameter	20 mg	40 mg	80 mg
NC_{max} (ng/ml•kg•mg)			
Males	0.0011 ± 0.0006	0.0011 ± 0.0006	0.0012 ± 0.0010
Females	0.0010 ± 0.0007	0.0011 ± 0.0005	0.0009 ± 0.0005
$NAUC_{0-72hr}$ (ng•hr/ml•kg•mg)			
Males	0.0215 ± 0.0107	0.0214 ± 0.0111	0.0254 ± 0.0150
Females	0.0163 ± 0.0084	0.0196 ± 0.0075	0.0195 ± 0.0101

Lovastatin Acid

Parameter	20 mg	40 mg	80 mg
NC_{max} (ng/ml•kg•mg)			
Males	0.0010 ± 0.0006	0.0012 ± 0.0012	0.0009 ± 0.0006
Females	0.0015 ± 0.0009	0.0015 ± 0.0013	0.0016 ± 0.0012
$NAUC_{0-72hr}$ (ng•hr/ml•kg•mg)			
Males	0.0244 ± 0.0156	0.0234 ± 0.0143	0.0259 ± 0.0178
Females	0.0277 ± 0.0220	0.0280 ± 0.0218	0.0300 ± 0.0209

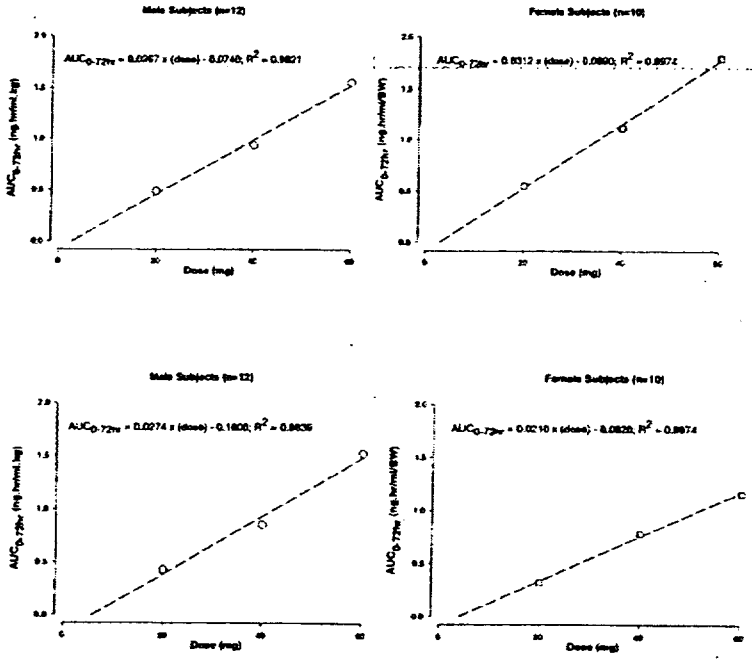


Figure 3 Linear regression between doses and normalized C_{max}

Reanalysis of dose proportionality was conducted with individual study data and pooled data because dose linearity was evaluated with two different parameters across studies. Power model between doses and C_{max} or AUC could be used for estimation of dose proportionality. Also, sameness test of clearance between doses would be reasonable method because clearance is a dose normalized parameter.

According to the results of power model, Altocor appears to have dose linearity between 10, 20, 40, and 60 mg doses because slope for lovastatin doses and AUC are close to 1 and 90% confidence interval included slope 1. Results are summarized in the following figure and table.

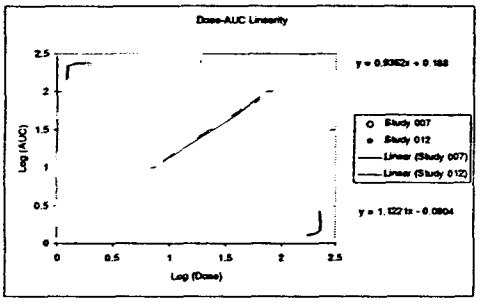


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Figure 4 Relationship between doses and AUCs in power model

Table VIII Summary of slopes and CI in power model

	Study 007	Study 012	Total
Slope	0.936	1.122	1.038
intercept	0.188	-0.090	0.045
r^2	0.4076	0.4658	0.50

Also, it is concluded that the means of dose normalized AUCs are not significantly different between doses at alpha=0.05. Distribution of the parameters is shown in the following figure.

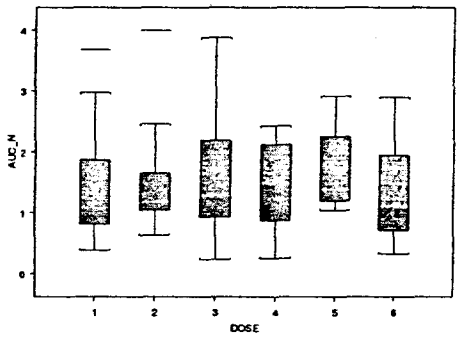

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Figure 5 Distribution of dose normalized AUCs (Label of X-axis are 1=20mg, 2=40mg, and 3=60mg in Study 012, 4=10mg, 5=20mg, and 6=40 mg in Study 007)

In conclusion, Altocor seemed to have dose linearity between 10-60 mg.

- **What are the basic PK parameters ?**

Pharmacokinetics was characterized in single dose studies and in a multiple daily doses study compared to that of Mevacor. Single dose studies were conducted under fed (N=8, healthy male, Study 146-001) and overnight fasting conditions (N=24, healthy male, Study 146-103). Third one is pharmacokinetic characterization after multiple daily doses (N=23; 11 males, 12 females, Study 146-006).

The two single dose studies were phase I, single-centered, open-label, randomized, two-period crossover studies with proper washout period. Study medications (40 mg Altocor or Mevacor) were administered immediately after dinner or after overnight fasting condition. The dinner consisted of French dip with au jus, baked potato with margarine and sour cream, tossed salad with dressing, fruit cocktail, vanilla iced cookie, and 2x240 mL of 2% milk. Blood samples were drawn up to 24 hours after dosing for the study 001 and up to 48 hours after dosing for the study 103.

The plasma concentration-time profiles are shown in Figure 6 and 7.

Lovastatin Lovastatin acid

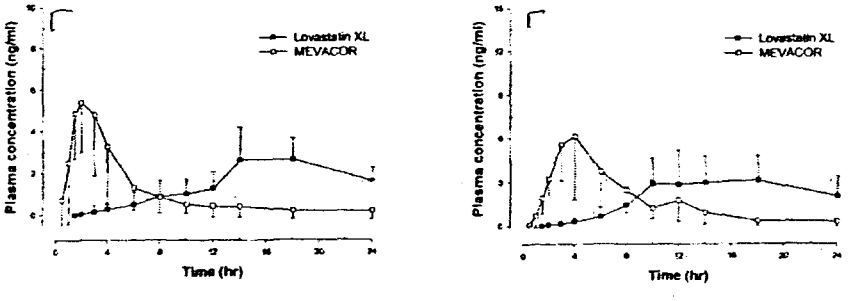

Figure 6 Plasma concentration-time profiles under fed condition

Lovastatin Lovastatin acid

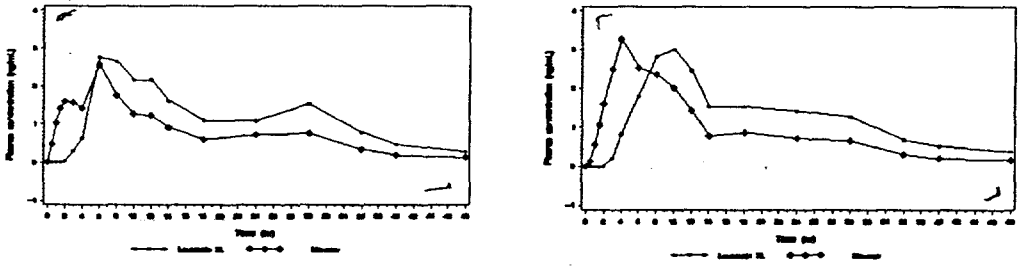

Figure 7 Plasma concentration-time profiles under fasting condition

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Delayed or controlled release characteristics were demonstrated in the studies compared with Mevacor with significantly longer T_{max} and lower C_{max}. Relative lovastatin bioavailability of Altocor was 141% and 151% as reference of Mevacor under fed and fasting condition, respectively, after 40 mg single dose. The corresponding values of lovastatin acid were 114% and 133% under fed and fasting conditions, respectively. Pharmacokinetic parameters after single dose are summarized in the following table.

Table IX Summary of pharmacokinetic parameters after single dose

		AUC (ng hr/ml)		C_{max} (ng/ml)		T_{max} (hr)	
		Altocor	Mevacor	Altocor	Mevacor	Altocor	Mevacor
under fed (AUC_{0-24hr})	Lovastatin	33.9±11.8	26.6±17.0	3.15±1.24	6.13±2.56	15.5±5.1	2.1±0.6
	Lovastatin acid	47.5±18.9	42.2±20.3	4.64±1.89	6.45±4.09	13.8±3.8	3.9±1.0
under fasting (AUC_{0-48hr})	Lovastatin	54.2±20.4	37.6±17.5	3.39±1.39	2.80±1.15	10.4±7.8	5.1±2.2
	Lovastatin acid	58.0±20.0	44.4±17.2	3.37±1.91	3.75±1.81	11.2±5.1	5.6±2.5

Table X Mean values of T_{max} and Geometric Mean Ratio (Altocor/Mevacor) of C_{max} and AUC after Altocor single dose administration

		Lovastatin	Lovastatin acid
the fed condition	C_{max}	0.51	0.77
	AUC_{0-24hr}	1.41	1.14
	T_{max} (hr)	15.5	13.8
the fasting condition	C_{max}	1.21	0.89
	AUC_{0-48hr}	1.51	1.33
	T_{max} (hr)	10.4	11.2

A multiple dose study was a phase II, single-center, single-blind, randomized, positive-controlled two-way crossover design study with a 4-week diet/placebo run-in period and 2 active treatment periods that lasted 4 weeks each. Lovastatin 40-mg was administered as Altocor in the evening at approximately 10:00 p.m., at least one-half hour before bedtime, or MEVACOR with the evening meal at approximately 6:00 pm.

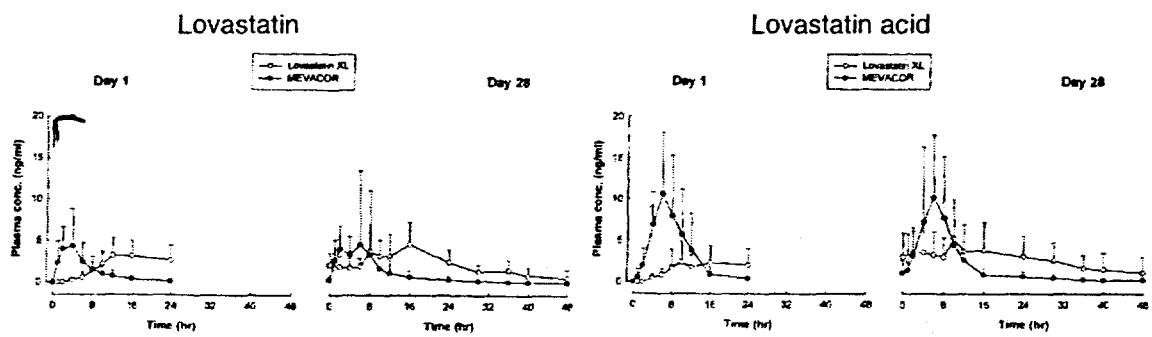


Figure 8 Plasma concentration-time profiles after the multiple daily doses

Results after multiple doses were compatible with the single dose studies for delayed or controlled release characteristics. There was accumulation after Altocor multiple daily doses and it was expected with significant contribution of $AUC_{24-48hr}$ to the total AUC. Trough concentration after multiple doses is an important measure of efficacy and/or safety. Although C_{24} was significantly increased after Altocor administration, there was no further safety concern in the study with 40 mg. In general, pharmacokinetic characteristics in patients remains compatible with that of healthy volunteers based on comparison cross studies except higher AUC for lovastatin acid. Pharmacokinetic parameters after multiple daily doses are summarized in the following table.

Table XI Summary of pharmacokinetic parameters after multiple daily doses

		AUC_{0-24hr} (ng hr/ml)		C_{max} (ng/ml)		C_{min} (ng/ml)	
		Altocor	Mevacor	Altocor	Mevacor	Altocor	Mevacor
Day 1	Lovastatin	49.9±23.5	33.7±21.6	4.0±2.0	6.7±4.0		
	Lovastatin acid	38.6±31.4	84.1±63.1	2.9±2.5	11.7±6.9		
	Total inhibitor	136.3±73.3	226.9±100.4	10.5±5.8	31.4±9.4		
	Active inhibitor	83.3±44.7	178.9±82.9	6.4±4.3	22.4±6.6		
Day 28	Lovastatin	76.6±36.9 (1.48)	44.7±46.2 (1.15)	5.5±2.5 (1.36)	7.8±8.1 (1.00)	2.6±1.6	0.4±0.4
	Lovastatin acid	87.1±67.2 (1.88)	82.5±60.3 (1.00)	5.8±4.8 (1.70)	11.9±10.2 (0.91)	3.1±2.5	0.7±0.6
	Total inhibitor	262.6±159.4 (1.81)	251.6±154.1 (1.06)	17.3±8.1 (1.71)	36.2±20.7 (1.05)		
	Active inhibitor	171.3±122.9 (1.86)	185.9±100.4 (1.02)	13.4±9.1 (2.06)	26.6±14.2 (1.09)		

Values in parenthesis: ratio between Day1 and Day 28

Table XII Geometric Mean Ratio (Altocor/Mevacor) of C_{max} and AUC, T_{max} after Altocor multiple daily doses administration

		Lovastatin	Lovastatin acid
Geometric Mean Ratio (Altocor/Mevacor)	C_{max}	0.84	0.43
	AUC_{0-24hr}	1.91	0.86
Accumulation Ratio	C_{max}	1.36	1.70
	AUC_{0-24hr}	1.48	1.88
	C_{24}	6.4	4.7

IV-C. General Biopharmaceutics

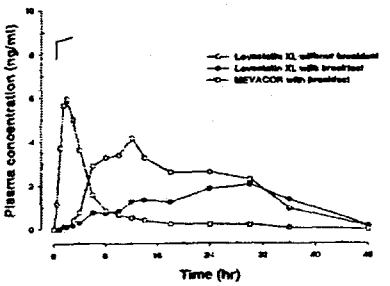
- **What is the effect of food on the bioavailability of lovastatin from Altocor ?**

The study (Study 146-002) was a phase I, open-label, single-center, single-dose, randomized, three-period crossover design (N=9, all Caucasian). Subjects were randomized to receive one of the following treatments: Treatment A, 40-mg Altocor after an overnight fast, Treatment B, 40-mg Altocor following a standard high fat breakfast, or Treatment C, 40-mg tablet of MEVACOR following a standard breakfast.

Exposures of lovastatin and lovastatin acid for Altocor were significantly lower with breakfast. The geometric mean ratios of AUC_{0-48hr} and C_{max} after breakfast were 0.60 and 0.61 compared to those under overnight fasting condition. Mean of T_{max} also significantly increased after the meal compared to that under fasting (24.0 hour vs. 11.1 hour). There was no dose-dumping phenomenon after the breakfast.

Plasma concentration-time profiles are shown and pharmacokinetic parameters are summarized in the following figures and tables, respectively.

Lovastatin



Lovastatin acid

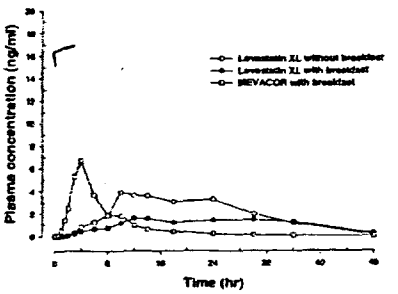


Figure 9 Plasma concentration-time profile after Altocor (food effect)

Table XIII Summary of pharmacokinetic parameters (food effect)

Lovastatin

Treatment	AUC_{0-48hr} (ng•hr/ml)	C_{max} (ng/ml)	T_{lag} (hr)	T_{max} (hr)
Lovastatin XL without breakfast	90.0 ± 50.0	4.86 ± 1.99	1.9 ± 0.6	11.1 ± 5.8
Lovastatin XL after breakfast	54.7 ± 27.7	3.09 ± 1.48	2.7 ± 1.1	24.0 ± 7.9
MEVACOR after breakfast	33.1 ± 10.4	6.72 ± 2.75	0.1 ± 0.2	2.4 ± 0.9
Geometric Mean Ratio*	2.61	0.76	-	-
Geometric Mean Ratio*	1.56	0.46	-	-
Geometric Mean Ratio*	0.60	0.61	-	-

* Ratio = Lovastatin XL without breakfast/MEVACOR after breakfast
* Ratio = Lovastatin XL after breakfast/MEVACOR after breakfast
* Ratio = Lovastatin XL after breakfast/Lovastatin XL without breakfast

Lovastatin Acid (β-hydroxyacid of lovastatin)

Treatment	AUC_{0-48hr} (ng•hr/ml)	C_{max} (ng/ml)	T_{lag} (hr)	T_{max} (hr)
Lovastatin XL without breakfast	91.2 ± 59.6	4.90 ± 2.32	2.1 ± 0.4	14.7 ± 5.9
Lovastatin XL after breakfast	50.3 ± 35.6	2.50 ± 1.45	2.8 ± 1.0	20.9 ± 7.8
MEVACOR after breakfast	41.6 ± 35.1	6.88 ± 5.81	0.3 ± 0.3	3.6 ± 0.7
Geometric Mean Ratio*	2.31	0.76	-	-
Geometric Mean Ratio*	1.24	0.38	-	-
Geometric Mean Ratio*	0.54	0.49	-	-

* Ratio = Lovastatin XL without breakfast/MEVACOR after breakfast
* Ratio = Lovastatin XL after breakfast/MEVACOR after breakfast
* Ratio = Lovastatin XL after breakfast/Lovastatin XL without breakfast

In a comparison of AUCs across studies, exposure as AUC_{0-24hr} of lovastatin was 30% lower after breakfast compared to that after dinner for Altocor: 23.7 vs. 33.9 ng hr/ml. In the same studies, exposure was increased 15% for Mevacor. Differences in food appear to be a major factor to explain the above results because chronological difference of lovastatin has not been recognized up to now. The breakfast consisted of: one buttered English muffin, one slice of American cheese, one fried egg, one slice of Canadian bacon, 2.45 ounces of has brown potatoes, eight fluid ounces of whole milk, and six fluid ounces of orange juice.

Comparison across studies also indicated that relative bioavailability of Altocor might be related to mealtime. The values of AUC_{0-24hr} (ng hr/ml) were 42.75 administration of bedtime (about 10 PM) and 33.9 for administration immediately after dinner.

It is expected that foods increase lovastatin bioavailability of Mevacor and decrease that of Altocor according to the above study results (Study 002). Based on AUC comparison across studies (i.e., Study 001 vs. 103), it appears to be no food effect on both formulations. Factor to explain this particular inconsistency is not known.

- **Is dosage form equivalent established among 10, 20, 40, and 60 mg ?**

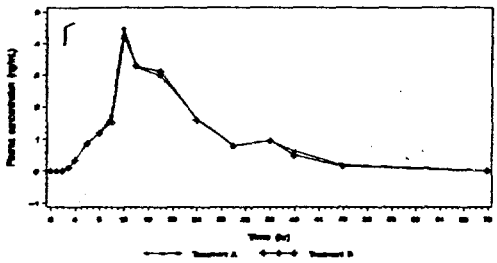
Dose proportionality was established with one 10 mg, one 20 mg, and one 40 mg tablets. Therefore it is concluded that those are equivalent. Dosage form equivalence between one 60 mg tablet and one 20 mg and one 40 mg was investigated in a PK study.

The study was a phase I, single-center, open-label, single-dose, randomized, tow-period crossover study in healthy male volunteers (N=24, Study 146-102). Subjects were administered

either Altocor as one 60 mg tablet or as one 20 mg tablet + one 40 mg tablet with 240 mL of water (at room temperature) at approximately 10:00 pm.

The plasma concentration-time profiles and pharmacokinetic parameters are summarized in the following figures and tables.

Lovastatin



Lovastatin acid

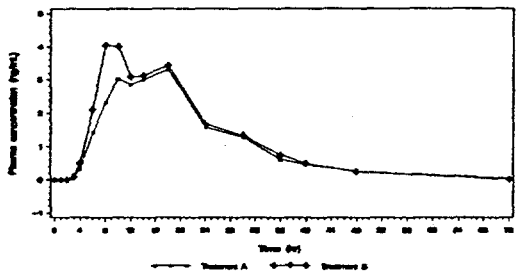


Figure 10 Plasma concentration-time profiles in the study of dosage form equivalence study

Table XIV Mean SD values of pharmacokinetic parameters – lovastatin (Study 102)

Parameter	Lovastatin XL 60 mg	Lovastatin XL 20 mg + 40 mg	Relative Bioavailability[a]	90% Confidence Interval
C_{max} (ng/mL)	4.94 ± 2.51	4.43 ± 1.81	107%	(98.4%, 117.4%)
AUC_{0-72hr} (ng•hr/mL)	68.5 ± 33.6	66.4 ± 28.8	102%	(87.7%, 119.6%)
AUC_{0-inf} (ng•hr/mL)	72.2 ± 34.9	69.3 ± 33.1	100%	(80.0%, 124.6%)
T_{lag} (hr)	3.3 ± 1.3	3.0 ± 1.0	–	
T_{max} (hr)	14.1 ± 2.9	13.4 ± 2.5	–	
$t_{½}$ (hr)	4.4[b]	5.4[b]	–	

[a] Least square mean ratio of Lovastatin XL 60 mg/Lovastatin XL 20 mg + 40 mg
[b] Harmonic mean

Table XV Mean SD values of pharmacokinetic parameters – lovastatin acid (Study 102)

Parameter	Lovastatin XL 60 mg	Lovastatin XL 20 mg + 40 mg	Relative Bioavailability[a]	90% Confidence Interval
C_{max} (ng/mL)	4.16 ± 2.61	5.06 ± 5.04	93%	(82.2%, 104.5%)
AUC_{0-72hr} (ng•hr/mL)	72.9 ± 43.6	82.9 ± 70.5	94%	(83.8%, 106.5%)
AUC_{0-inf} (ng•hr/mL)	76.6 ± 46.3	82.1 ± 80.4	98%	(82.2%, 117.5%)
T_{lag} (hr)	3.5 ± 1.0	3.2 ± 0.9	–	
T_{max} (hr)	14.3 ± 3.9	12.7 ± 4.6	–	
$t_{½}$ (hr)	6.0[b]	5.7[b]	–	

[a] Least square mean ratio of Lovastatin XL 60 mg/Lovastatin XL 20 mg + 40 mg
[b] Harmonic mean

The mean values of C_{max} and AUC_{0-72hr} were within BE range in 90% confidence interval and thus it is concluded that the dosage forms are equivalent.

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- **How do the dissolution conditions and specifications assure quality of the product ?**

Dissolution profiles were reported under the following condition: USP apparatus 2 (paddle) at 50 rpm, medium (900 mL) of ~ sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5 and temperature 37°C. Dissolution data from the above condition is summarized in the following table.

Table XVI Dissolution data

Strength	10	10	20	20	20	40	40	40	40	40	60	60
Lot	P98185	760R003	P98186	770R002	770R001	P98286	P97263	780R001	780R005	780R004	790R001	790R002
Study Protocol	007	009	007	102	012 009 010 011		001 002 006 007	102 009 010	103 012 102 011		102	
Time (hr)	% dissolved											
0.5	0		0			0	0					
1	1	3	0	0	5	1	1	2	0	0	0	0
2	6	21	4	9	25	13	12	16	9	8	4	5
3	21		16			30	29					
4	39	55	33	50	60	46	44	49	43	40	32	33
6	67		65			72	67					
8	80	82	82	83	84	83	80	83	82	78	76	76
12	86	88	89	89	91	88	86	88	88	86	85	85
16	88		92			89	90					
20	89		92			89	92					

The sponsor proposed the following specification:

Time (hr)	Amount Dissolved (%)
—	~
2	—
8	—
16	—

NMT: Not more than
NLT: Not less than

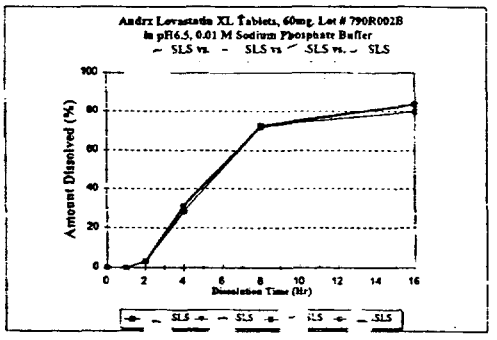
There was no significant difference in dissolution profiles between paddle speed of 50 and 75 rpm, and among — concentrations of ——— Therefore, it is recommended using — concentration of — in the dissolution condition.

The proposed dissolution method and specification does not assure delayed release characteristic for Altocor. Therefore, it is recommended to establish new dissolution method and specification accordingly to assure both delayed and extended characteristics of the formulation.

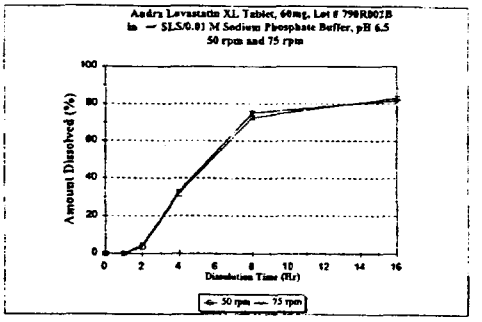
The following specification is recommended as an interim basis until the new dissolution method and specification established for quality control.

Time (hr)	Amount Dissolved (%)
2	—
8	—
—	—

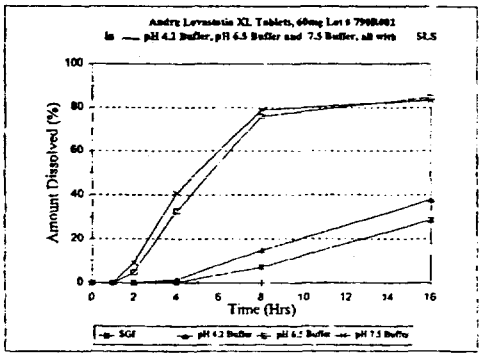
Dissolution profiles of 60 mg Altocor in various conditions are shown in the following figures.



Concentration



R.P.M.



pH

Figure 11 Effect of —— concentration, rpm, and pH on dissolution of 60 mg Altocor

IV-D. Analytical Section

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Proposed Label and Reviewer's Comments

The following is the sponsor's proposed labeling for lovastatin XL (ALTOCOR™)that was submitted to the NDA. This Reviewer's comments will appear in test boxes in the appropriate sections and are not intended to appear in the final label. Recommended changes that are intended to appear in the final label will appear as edit track-changes within the labeling text. As labeling will likely be an ongoing discussion with the sponsor, the editing changes and comments below may be altered as a result of these discussions and should not be considered as final at this time.

PROPOSED TEXT OF THE LABELING

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Draft

Labeling

VI. Appendix
VI-A. Study Summary

Study No. 146-001

Title of study: A Single-dose (40 mg), Safety and Pharmacokinetic Study of Extended-Release Dosage Form of Lovastatin (Lovastatin XL) Relative to MEVACOR® in Healthy Male Subjects

Investigator: [redacted]

Study site: One study center in the United States

Publications (references): none

Studied period (days): 9 days **Phase of development:** I
Initiation date (first patient visit): 06-Aug-97
Completion date (last patient completed): 14-Aug-97

Objective: The objective of this study was to evaluate the safety and plasma profiles of the extended-release dosage form of lovastatin (Lovastatin XL) relative to Mevacor in healthy male subjects.

Methodology: This was a single-center, open-label, single-dose, randomized, two-period crossover study with a one-week washout period between the treatments. In each study period, either one 40 mg Lovastatin XL tablet or one 40 mg Mevacor tablet was administered orally to each subject after dinner.

Number of subjects (planned and analyzed):
Eight (8) subjects were planned, and 8 subjects were randomized. All 8 subjects completed the study.

Diagnosis and main criteria for inclusion: Healthy, non-smoking, male subjects between the ages of 18 and 45 years, whose body weights were within 10% of normal values (based on the 1983 [redacted] height/weight tables).

Test product, dose/strength/concentration and mode of administration, lot number(s): Patients were instructed to take one Lovastatin XL 40 mg tablet (Lot No. P97263), orally, after dinner each day.

Reference therapy, dose and mode of administration, lot number(s): Patients were instructed to take one Mevacor 40 mg tablet (Lot No. E1151), orally, after dinner each day.

Duration of treatment: Single dose x 2

Criteria for evaluation:

Efficacy: This study was not designed to evaluate efficacy.

Pharmacokinetic/Pharmacodynamic: The following pharmacokinetic parameters were determined for lovastatin and lovastatin acid: C_{max} (the observed maximum concentration), $AUC_{0\text{-}24hr}$ (area under the plasma concentration-time curve), T_{lag} (lag time), T_{max} (the observed time to reach the maximum concentration), and if possible, $t_{1/2}$ (the elimination half-life). The geometric mean ratios of Lovastatin XL/Mevacor were calculated for C_{max} and $AUC_{0\text{-}24hr}$.

Safety: Safety was evaluated by assessing the occurrence and frequency of adverse events, changes in vital signs, physical examinations, electrocardiograms (EKGs) and clinical laboratory values.

Data analysis methods: Plasma samples for lovastatin and its β-hydroxyacid were analyzed at — using a — method. No statistical analyses were applied to the pharmacokinetic data.

Summary/Conclusions:

Efficacy results: Not applicable

Pharmacokinetic Results: The mean ± SD pharmacokinetic data from 8 patients are summarized in the following tables:

Table 1. Mean ± SD Pharmacokinetic Data for Lovastatin

Parameters	Lovastatin XL	Mevacor	Geometric Mean Ratio[a]
C_{max} (ng/mL)	3.15 ± 1.24	6.13 ± 2.56	0.51
$AUC_{0\text{-}24hr}$ (ng•hr/mL)	33.9 ± 11.8	26.6 ± 17.0	1.41
T_{lag} (hr)	2.6 ± 1.0	0.3 ± 0.3	--
T_{max} (hr)	15.5 ± 5.1	2.1 ± 0.6	--

Source: Final Study Report
[a]Ratio: Lovastatin XL/Mevacor.

Table 2. Mean ± SD Pharmacokinetic Data for Lovastatin Acid (β-Hydroxyacid of Lovastatin)

Parameters	Lovastatin XL	Mevacor	Geometric Mean Ratio[a]
C_{max} (ng/mL)	4.64 ± 1.89	6.45 ± 4.09	0.77
$AUC_{0\text{-}24hr}$ (ng•hr/mL)	47.5 ± 18.9	42.2 ± 20.3	1.14
T_{lag} (hr)	2.5 ± 1.0	0.4 ± 0.4	--
T_{max} (hr)	13.8 ± 3.8	3.9 ± 1.0	--

Source: Final Study Report
[a]Ratio: Lovastatin XL/Mevacor.

The mean plasma concentration-time profiles of lovastatin were different for Lovastatin XL and Mevacor. Following Mevacor, lovastatin quickly appeared in plasma with a T_{lag} value of 0.3 hour. The mean maximum concentration (C_{max}), 6.13 ng/mL, occurred at about 2 hours and then declined to almost undetectable at 24 hours. In contrast, lovastatin following oral administration of Lovastatin XL had a delayed absorption with a T_{lag} value of 2.6 hours. The mean C_{max}, 3.15 ng/mL, was about one-half of that for Mevacor. The time (T_{max}) to reach the maximum plasma concentration was delayed (by about 16 hours compared to Mevacor). In addition, a significant plasma concentration of lovastatin was found 24 hours after dosing. The relative bioavailability of Lovastatin XL to Mevacor, in terms of $AUC_{0\text{-}24hr}$ ratio of lovastatin was 141%, indicating more drug was absorbed in the gastrointestinal tract from Lovastatin XL.

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Similar to lovastatin data, the mean plasma concentration-time profile of lovastatin acid for Lovastatin XL was different from that of Mevacor. On average, after administration of Mevacor, the maximum concentration of lovastatin acid in plasma, 6.45 ng/mL, was observed around 4 hours and then declined quickly. However, lovastatin acid, following administration of Lovastatin XL, was not detected until 2.5 hours. The mean C_{max} (4.64 ng/mL) and T_{max} (13.8 hr) values were lower and longer, respectively, than the respective values for Mevacor. The relative bioavailability of Lovastatin XL to Mevacor, in terms of AUC_{0-24hr} ratio of lovastatin acid, was 114%.

Safety results: Both Lovastatin XL and Mevacor were well tolerated by all subjects. There were no serious adverse events or discontinuations due to adverse events reported during the study. One (12.5%) patient in the Lovastatin XL treatment group and 1 (12.5%) patient in the Mevacor group each experienced 1 mild and unrelated treatment-emergent adverse event during the study (purpura and headache, respectively).

The majority of abnormal laboratory results were slightly outside the normal ranges. One patient, who had a high bilirubin value at Screening (2.0 mg/dL), experienced a total bilirubin value that was approximately 2.5 times the upper limit of normal (2.5 mg/dL) after receiving Lovastatin XL during Period I. This subject's total bilirubin value remained high after receiving Mevacor in Period II (2.3 mg/dL) and returned to baseline (1.7 mg/dL), 6 days after Period II dosing.

There were no clinically significant changes in physical examination, vital sign, EKG and clinical laboratory measurements over the course of the study. Specifically, there were no unwanted effects of gastrointestinal symptoms during the study.

Conclusions: All subjects tolerated the study medications (Lovastatin XL and Mevacor) well. Compared to Mevacor, Lovastatin XL exhibited delayed- and extended-release characteristics in terms of plasma concentration profiles of lovastatin and its active drug, lovastatin acid. The extended-release nature of Lovastatin XL was reflected by the lower C_{max} values and the prolonged profiles of plasma levels of both lovastatin and lovastatin acid. The pharmacokinetic data demonstrate that systemic availability of lovastatin and, to a slight degree, lovastatin acid after administration of Lovastatin XL was larger than those after administration of Mevacor, indicating that more drug was absorbed in the gastrointestinal tract after administration of Lovastatin XL compared to administration of Mevacor.

Date of report: January 20, 2000

Study No. 146-002

Title of study: A Morning Single-Dose, Safety and Pharmacokinetic Study of Lovastatin XL Relative to MEVACOR® in Healthy Male Subjects

Investigator: [redacted]

Study site: One study center in the United States

Publications (references): none

Studied period (days): 17 days
Initiation date (first patient visit): 25-Sept-97
Completion date (last patient completed): 11-Oct-97

Phase of development: I

Objectives: The objectives of this study were to evaluate *in-vivo* performance of Lovastatin XL after morning dosing, to determine the effects of food on oral absorption of Lovastatin XL, and to compare the pharmacokinetics of Lovastatin XL relative to Mevacor after morning dosing with breakfast.

Methodology: This was an open-label, single-center, single-dose, randomized, three-period crossover study with a one-week washout period between the treatments. In each study period, either one 40 mg Lovastatin XL tablet after an overnight fast, one 40 mg Lovastatin XL tablet after a standard breakfast, or one 40 mg Mevacor tablet after a standard breakfast, was administered orally to each subject.

Number of subjects (planned and analyzed): Nine (9) subjects were planned, and 9 subjects were randomized. All 9 subjects completed the study.

Diagnosis and main criteria for inclusion: Healthy, non-smoking, male subjects between the ages of 18 and 45 years, whose body weights were within 10% of normal values (based on the 1983 [redacted] height/weight tables).

Test product, dose/strength/concentration and mode of administration, lot number(s): Patients were instructed to take one Lovastatin XL 40 mg tablet (Lot No. P97263) orally after an overnight fast, or one Lovastatin XL 40 mg tablet (Lot No. P97263) orally after a standard breakfast each day.

Reference therapy, dose and mode of administration, lot number(s): Patients were instructed to take one Mevacor 40 mg (Lot No. E1151) tablet orally following a standard breakfast each day.

Duration of treatment: Single dose x 3

Criteria for evaluation:

Efficacy: This study was not designed to evaluate efficacy.

Pharmacokinetic/Pharmacodynamic: The following pharmacokinetic parameters were determined for lovastatin and lovastatin acid: $AUC_{0\text{-}48hr}$ (area under the plasma concentration-time curve), C_{max} (the observed maximum concentration), T_{lag} (lag time), and T_{max} (the observed time to reach the maximum concentration), and if possible, $t_{1/2}$ (the elimination half-life). The ratios of Lovastatin XL without breakfast/Mevacor, Lovastatin XL after breakfast/Mevacor, and Lovastatin XL after breakfast/Lovastatin XL without breakfast were calculated for C_{max} and $AUC_{(0\text{-}48hr)}$.

Safety: Safety was evaluated by assessing the occurrence and frequency of adverse events, changes in vital signs, physical examinations, electrocardiograms (EKGs) and clinical laboratory values.

Data analysis methods: Plasma samples for lovastatin and its β-hydroxyacid were analyzed at —— —— using a pre-validated —— method. No statistical analyses were applied to the pharmacokinetic data.

Summary/Conclusions:

Efficacy results: Not applicable

Pharmacokinetic Results: The mean ± SD pharmacokinetic data from 9 patients are summarized in the following tables:

Table 1. Mean ± SD Values of Lovastatin

Treatment	$AUC_{0-\infty}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{lag} (hr)	T_{max} (hr)
Lovastatin XL without breakfast	90.0 ± 50.0	4.86 ± 1.99	1.9 ± 0.6	11.1 ± 5.8
Lovastatin XL after breakfast	54.7 ± 27.7	3.09 ± 1.48	2.7 ± 1.1	24.0 ± 7.9
Mevacor after breakfast	33.1 ± 10.4	6.72 ± 2.75	0.1 ± 0.2	2.4 ± 0.9
Geometric Mean Ratio[a]	2.61	0.76	–	–
Geometric Mean Ratio[b]	1.56	0.46	–	–
Geometric Mean Ratio[c]	0.60	0.61	–	–

Source: Final Study Report
[a]Ratio = Lovastatin XL without breakfast/Mevacor after breakfast
[b]Ratio = Lovastatin XL after breakfast/Mevacor after breakfast
[c]Ratio = Lovastatin XL after breakfast/Lovastatin XL without breakfast

Table 2. Mean ± SD Values of Lovastatin Acid (β-hydroxyacid of lovastatin)

Treatment	$AUC_{0-\infty}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{lag} (hr)	T_{max} (hr)
Lovastatin XL without breakfast	91.2 ± 59.6	4.90 ± 2.32	2.1 ± 0.4	14.7 ± 5.9
Lovastatin XL after breakfast	50.3 ± 35.6	2.50 ± 1.45	2.8 ± 1.0	20.9 ± 7.8
Mevacor after breakfast	41.6 ± 35.1	6.88 ± 5.81	0.3 ± 0.3	3.6 ± 0.7
Geometric Mean Ratio[a]	2.31	0.76	–	–
Geometric Mean Ratio[b]	1.24	0.38	–	–
Geometric Mean Ratio[c]	0.54	0.49	–	–

Source: Final Study Report
[a]Ratio = Lovastatin XL without breakfast/Mevacor after breakfast
[b]Ratio = Lovastatin XL after breakfast/Mevacor after breakfast
[c]Ratio = Lovastatin XL after breakfast/Lovastatin XL without breakfast

The mean plasma concentration-time profiles of lovastatin were different among three treatment groups. In subjects receiving Lovastatin XL after or without breakfast, lovastatin was not observed in central circulation until 1 to 3 hours postdose, and then maintained a relatively constant plasma level for about 30 hours. Both profiles are typical for extended-release formulations. However, in the same subjects receiving Mevacor after breakfast, lovastatin rapidly appeared in systemic circulation and then its plasma concentrations declined. Only very low plasma concentrations of lovastatin were still detectable at 12 hours after dosing.

On average, the $AUC_{0\text{-}48hr}$ values of lovastatin in subjects receiving Lovastatin XL after and without breakfast (54.7 and 90.0 ng•hr/mL, respectively) were greater than that (33.1 ng•hr/mL) in the same subjects receiving Mevacor after breakfast. The corresponding C_{max} values were lower (3.09 and 4.86 ng/mL versus 6.72 ng/mL), while the corresponding T_{max} values were much longer (24.0 and 11.1 hours versus 2.4 hours) and the corresponding $t_{1/2}$ values were shorter (4.3 and 4.4 hours versus 9.4 hours). However, these half-lives may be misleading due to the inability of calculating the individual $t_{1/2}$ values for the majority of subjects.

The geometric mean ratios of $AUC_{0\text{-}48hr}$ and C_{max} for lovastatin were 2.61 and 0.76 when comparing the treatment of Lovastatin XL without breakfast with Mevacor after breakfast, while the corresponding values were 1.56 and 0.46 when comparing Lovastatin XL after breakfast with Mevacor after breakfast.

The geometric mean ratios of $AUC_{0\text{-}48hr}$ and C_{max} for lovastatin were 0.60 and 0.61 when comparing the treatment of Lovastatin XL after breakfast with the same treatment without breakfast in the same subjects. Thus, it can be concluded that a standard breakfast reduced the rate and extent of absorption into the systemic circulation of lovastatin from Lovastatin XL.

The plasma concentration-time profile of lovastatin acid for each treatment was similar to that of lovastatin. The mean $AUC_{0\text{-}48hr}$ values of lovastatin acid in subjects receiving Lovastatin XL after and without breakfast (50.3 and 91.2 ng•hr/mL, respectively) were greater than that (41.6 ng•hr/mL) in the same subjects receiving Mevacor after breakfast. Together with the greater $AUC_{0\text{-}48hr}$ value of lovastatin mentioned above, this result indicated that the systemic bioavailability of unchanged lovastatin and lovastatin acid was increased by the extended-release formulation. This differed from Mevacor, which produced a mean lovastatin $AUC_{0\text{-}48hr}$ value that was less than the mean lovastatin acid $AUC_{0\text{-}48hr}$ value.

The geometric mean ratios of $AUC_{0\text{-}48hr}$ and C_{max} for lovastatin acid were similar to those for lovastatin when comparing Lovastatin XL without breakfast with Mevacor after breakfast or with Lovastatin XL after breakfast.

The mean terminal elimination half-lives of lovastatin acid in subjects receiving separately Lovastatin XL without breakfast, Lovastatin XL after breakfast, and Mevacor after breakfast were 5.4, 6.0 and 6.3 hours, respectively. Similar to the half-lives of lovastatin, these values are not reliable because the individual half-lives could not be determined from the majority of subjects.

Safety results: Both Lovastatin XL and Mevacor were well tolerated by all subjects. There were no serious adverse events or discontinuations due to adverse events reported during the study. One (11.1%) subject experienced unrelated headache (mild) and nausea (moderate) 6 days and 6 hours after receiving Lovastatin XL after an overnight fast, that resolved 9 hours after subsequent dosing of Mevacor. There were no adverse effects of the gastrointestinal tract during the study.

The majority of abnormal laboratory results were slightly outside of the normal ranges. Two subjects experienced elevations in AST (49 u/L and 44 u/L) and ALT (82 u/L and 78 u/L) values, respectively, after receiving Lovastatin XL without breakfast. AST returned to normal and ALT was only slightly elevated (47 u/L) after Treatment Phase II for one subject, while the other subject's AST and ALT values were still elevated at the initial discharge laboratory evaluation (48 u/L and 86 u/L, respectively, and 38 u/L and 77 u/L, respectively upon repeat). The subject was lost to follow-up, having moved out of state. Both incidences of elevated AST and ALT were considered drug related, but not clinically significant. There were no clinically significant changes in the clinical laboratory measurements, physical examinations, vital signs or EKGs over the course of the study.

Conclusions: Both Lovastatin XL and Mevacor were well tolerated by all participants. Lovastatin XL exhibited a delayed- and extended-release characteristic *in vivo*. The systemic availability of lovastatin after administration of Lovastatin XL was larger than that after Mevacor, indicating more drug was absorbed in the gastrointestinal tract from Lovastatin XL compared to Mevacor. Ingestion of a standard breakfast reduced the bioavailability of Lovastatin XL by approximately 40-50%.

Date of report: December 14, 1998

Study No. 146-006*

Title of study: A Multiple-Dose Safety, Pharmacokinetic and Pharmacodynamic Study of Lovastatin XL Relative to MEVACOR®

Investigator: [redacted]

Study site: One study center in the United States

Publications (references): none

Studied period (days): 132 days **Phase of development:** II
Initiation date (first patient visit): 20-Jan-98
Completion date (last patient completed): 31-May-98

Objectives: The objectives of this study were: 1) to evaluate the short-term safety and tolerability of Lovastatin XL compared with Mevacor, and 2) to evaluate the pharmacokinetics/pharmacodynamics of Lovastatin XL compared with Mevacor after administration of the first dose of either agent and multiple doses of either agent, when steady state plasma concentrations of lovastatin were attained.

Methodology: This was a single-center, single-blind, randomized, positive-controlled, two-way crossover design study with a 4-week diet/placebo run-in period and 2 active treatment periods that lasted 4 weeks each. During treatment Period I, patients received either 40 mg/day of Lovastatin XL or 40 mg/day of Mevacor for 4 weeks, according to the randomization schedule. Prior to entering treatment Period II, patients entered a 2-week placebo washout period. During treatment Period II, each patient was switched to the alternate study medication for 4 weeks.

Plasma samples were obtained from those subjects participating in the pharmacokinetic substudy after the first dose of each active treatment [Visit 3 (randomization) in Period I and Visit 6 in Period II], and again following the last dose of each active treatment period (Visits 5 and 8).

Number of subjects (planned and analyzed):

Planned: 24 overall (12 in the pharmacokinetic substudy)

Randomized: 26 overall (13 in the pharmacokinetic substudy)

Completed: 23 overall (12 in the pharmacokinetic substudy)

Diagnosis and main criteria for inclusion: Men and women 21 to 65 years of age with hypercholesterolemia with fasting plasma low-density lipoprotein cholesterol (LDL-C) levels between 130 and 250 mg/dL and a fasting plasma triglyceride level <350 mg/dL at Visit 2.

Test product, dose/strength/concentration and mode of administration, lot number(s): Patients were instructed to take Lovastatin XL 40 mg (Lot No. P97263) tablets orally once a day in the evening (10:00 p.m.), at least one-half hour before bedtime.

Reference therapy, dose and mode of administration, lot number(s): Patients were instructed to take Mevacor 40 mg (Lot No. E1151) tablets orally once a day in the evening (6:00 p.m.) with the evening meal.

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Duration of treatment: 8 weeks

Criteria for evaluation:

Efficacy: The primary efficacy evaluation was the reduction of LDL-C after combining 3- and 4-weeks of treatment with Lovastatin XL or Mevacor, given once daily. Other efficacy evaluations included the reduction of total cholesterol and triglycerides and the increase in high-density lipoprotein cholesterol (HDL-C).

Pharmacokinetic/Pharmacodynamic: The pharmacokinetic parameters [C_{max}, $AUC_{0\text{-}24hr}$, $t_{1/2}$ and R (accumulation ratio)] were determined for lovastatin, lovastatin acid, and total and active inhibitors of HMG-CoA reductase. The ratios of Lovastatin XL/Mevacor were calculated for C_{max} and $AUC_{0\text{-}24hr}$.

Safety: Safety was evaluated by assessing the occurrence and frequency of adverse events, changes in vital signs, physical examinations, and clinical laboratory values.

Statistical methods: A repeated measures analysis of variance (ANOVA) model was used to analyze the changes from baseline of each efficacy variable after 3-week treatment at Visit 4 and after 4-week treatment at Visit 5 in Period I, or at Visits 7 and 8 in Period II. The model included factors sequence, subject (sequence), treatment, week, sequence-by-treatment, subject-by-treatment (sequence), week, sequence-by-week, subject-by-week (sequence), treatment-by-week, and sequence-by-treatment-by-week. If the interaction was not present ($p \geq 0.05$), then a reduced model, with all the insignificant interaction terms dropped from the model (except sequence-by-treatment), was used to reanalyze the Weeks 3 and 4 data. The least squares means of percent changes for each treatment and treatment difference were obtained. If there was a treatment-by-week interaction, an indication of inappropriateness of combining Weeks 3 and 4 data, then no further analysis repeat measurement was carried out. A standard crossover model with sequence, subject (sequence) with period and treatment as the factors was used to analyze the Weeks 3 (Visit 4 or Visit 7) and 4 (Visit 5 or Visit 8) data separately. The residuals were tested for normality. Where significant deviation from normality was found, the analysis was also performed on the overall relative ranks.

No statistical analysis was applied to the pharmacokinetic data.

Summary/Conclusions:

Efficacy results: The data presented in this section is based on all patients who took at least one dose of active study medication and had at least one post baseline lipid evaluation. Lovastatin XL lowered LDL-C by 4.41 percentage points more ($p=0.0605$) than Mevacor at Week 3, by 3.62 percentage points more ($p=0.0737$) at Week 4, and by 3.87 percentage points more ($p=0.0435$) when Weeks 3 and 4 were combined (Table 1). The analysis of the combined Weeks 3 and 4 LDL-C data was pre-planned in the analysis plan.

Table 1. Least squares means of % LDL-C reduction

All patients	Lovastatin XL	Mevacor	Difference	p-value
Week 3 (n=24)	-40.60	-36.19	4.41	0.0605
Week 4 (n=22)	-42.48	-38.86	3.62	0.0737
Weeks 3 & 4 (n=24)	-41.32	-37.45	3.87	0.0435

Source: Final Study Report

When compared with Mevacor, Lovastatin XL increased HDL-C by 2.67 percentage points more (p=0.2588) at Week 3, by 3.04 percentage points more (p=0.2741) at Week 4 of each treatment period, and by 3.01 percentage points more (p=0.1402) when Weeks 3 and 4 were combined. Lovastatin XL lowered total cholesterol by 3.36 percentage points more than Mevacor (p=0.0245) at Week 3, by 1.67 percentage points more (p=0.3422) at Week 4, and by 2.48 percentage points more (p=0.0721) when Weeks 3 and 4 were combined. When compared to Mevacor, Lovastatin XL decreased triglycerides by 10.20 percentage points more (p=0.1067) at Week 3, but decreased triglycerides 3.12 percentage points less (p=0.5297) at Week 4.

Table 2. Mean percent change[a] in HDL-C, Total Cholesterol and Triglycerides

All patients included	Lovastatin XL	Mevacor	Difference	p-value
HDL-C				
Week 3 (n=24)	+7.73	+5.06	+2.67	0.2588
Week 4 (n=22)	+8.81	+5.77	+3.04	0.2741
Weeks 3 & 4 (n=24)	+8.19	+5.18	+3.01	0.1402
Total Cholesterol				
Week 3 (n=24)	-27.80	-24.44	-3.36	0.0245*
Week 4 (n=22)	-29.27	-27.60	-1.67	0.3422
Weeks 3 & 4 (n=24)	-28.48	-25.99	-2.48	0.0721
Triglycerides				
Week 3 (n=24)	-20.53	-10.33	-10.20	0.1067
Week 4 (n=22)	-21.02	-24.14	+3.12	0.5297

[a] Least squares means
*significant at p<0.05
Source: Final Study Report

Pharmacokinetic Results: The mean ± SD pharmacokinetic data from 12 patients are summarized in the following tables:

Table 3. Mean ± SD Values of C_{max} (ng/mL or ng eq/mL)

	Lovastatin XL			Mevacor		
	Day 1	Day 28	R*	Day 1	Day 28	R*
Lovastatin	4.0 ± 2.0	5.5 ± 2.5	1.36	6.7 ± 4.0	7.8 ± 8.1	1.00
Lovastatin acid	2.9 ± 2.5	5.8 ± 4.8	1.70	11.7 ± 6.9	11.9 ± 10.2	0.91
Total inhibitors of HMG-CoA reductase	10.5 ± 5.8	17.3 ± 8.1	1.71	31.4 ± 9.4	36.2 ± 20.7	1.05
Active inhibitors of HMG-CoA reductase	6.4 ± 4.3	13.4 ± 9.1	2.06	22.4 ± 6.6	26.6 ± 14.2	1.09

Source: Final Study Report
*R = Geometric mean ratio of C_{max} on Day 28 to that on Day 1.

Table 4. Mean ± SD Values of $AUC_{0\text{-}24hr}$ (ng•hr/mL or ng eq•hr/mL)

	Lovastatin XL			Mevacor		
	Day 1	Day 28	R*	Day 1	Day 28	R*
Lovastatin	49.9 ± 23.5	76.6 ± 36.9	1.48	33.7 ± 21.6	44.7 ± 46.2	1.15
Lovastatin acid	38.6 ± 31.4	87.1 ± 67.2	1.88	84.1 ± 63.1	82.5 ± 60.3	1.00
Total inhibitors of HMG-CoA reductase	136.3 ± 73.3	262.6 ± 159.4	1.81	226.9 ± 100.4	251.6 ± 154.1	1.06
Active inhibitors of HMG-CoA reductase	83.3 ± 44.7	171.3 ± 122.9	1.86	178.9 ± 82.9	185.9 ± 100.4	1.02

Source: Final Study Report
*R = Geometric mean ratio of $AUC_{0\text{-}24hr}$ on Day 28 to that on Day 1.

Table 5. Geometric Mean C_{max} and AUC_{0-24hr} Ratios (Lovastatin XL/Mevacor)

	C_{max} Ratio		AUC_{0-24hr} Ratio	
	Day 1	Day 28	Day 1	Day 28
Lovastatin	0.62	0.84	1.49	1.91
Lovastatin acid	0.23	0.43	0.46	0.86
Total inhibitors of HMG-CoA reductase	0.29	0.48	0.56	0.96
Active inhibitors of HMG-CoA reductase	0.25	0.47	0.46	0.84

Source: Final Study Report

Ratios of C_{max} and AUC_{0-24hr} at Day 28 compared to Day 1 for Lovastatin XL were between 1.36 and 2.06 for all the pharmacokinetic parameters (lovastatin, lovastatin acid, and total and active inhibitors of HMG-CoA reductase), indicating an accumulation of lovastatin and its latent and active metabolites after chronic once-daily administration. In contrast, the corresponding C_{max} and AUC_{0-24hr} ratios between Day 28 and Day 1 after administration of Mevacor ranged from ——— , indicating that lovastatin, lovastatin acid, and its latent and active metabolites did not accumulate after multiple daily doses of Mevacor.

The C_{max} values on Day 1 and at steady state (Day 28) were lower for lovastatin, lovastatin acid, and total and active inhibitors after Lovastatin XL administration compared to Mevacor administration. This is consistent with the extended-release characteristics of Lovastatin XL.

When compared to Mevacor, Lovastatin XL had higher systemic bioavailability of inactive prodrug at steady state, reflected by the higher value (1.91) of the AUC ratio for lovastatin. However, the relative bioavailability of Lovastatin XL to Mevacor, in terms of AUC_{0-24hr} ratio of lovastatin acid or active or total inhibitors of HMG-CoA reductase at steady state was less than or close to 1. The higher bioavailability of the inactive drug (lovastatin) and similar bioavailability of the active drug (lovastatin acid) and metabolites as well as total inhibitors of HMG-CoA reductase at steady state for Lovastatin XL relative to Mevacor are believed to be due to the extended-release characteristics of Lovastatin XL.

Safety results: There were no serious adverse events or discontinuations due to adverse events reported during the study.

Overall, 12 (46.2%) patients in the Lovastatin XL group and 5 (19.2%) patients in the Mevacor group experienced at least one treatment-emergent adverse event during the study. The greatest number of patients experiencing at least one treatment-emergent adverse event was in the body as a whole system with 6 (23.1%) patients in the Lovastatin XL group and 1 (3.8%) patient in the Mevacor group reporting an adverse event. Within the body as a whole system, headache was the most commonly reported treatment-emergent adverse event (11.5% of the Lovastatin XL group and 3.8% of the Mevacor group). The majority of adverse events reported by patients receiving Lovastatin XL (9, 34.6%) and Mevacor (4, 15.4%) were considered mild in intensity.

A small number of patients in the Lovastatin XL group (4, 15.4%) and in the Mevacor group (2, 7.7%) experienced treatment-emergent adverse events that were considered trial drug related. The greatest number of patients experiencing at least one treatment-emergent adverse event that was considered trial drug related was in the body as a whole system, with 3 (11.5%) patients in the Lovastatin XL

group and 0 (0.0%) patients in the Mevacor group reporting an adverse event. Within the body as a whole system, abdominal pain was the most commonly reported treatment-emergent adverse event (7.7% of the Lovastatin XL group and 0.0% of the Mevacor group).

During treatment with Lovastatin XL, the mean increases in AST (SGOT) and ALT (SGPT) from baseline to Week 3 were 1.8 mU/mL and 1.4 mU/mL, respectively. At Week 4, the mean increases in AST (SGOT) and ALT (SGPT) were 1.7 mU/mL and 1.8 mU/mL, respectively. None of the individual AST or ALT values increased to 2 times the upper limit of normal (ULN). Comparatively, during treatment with Mevacor the mean increases from baseline to Week 3 in AST (SGOT) and ALT (SGPT) were 1.4 mU/mL and 0.1 mU/mL, respectively. At Week 4, the mean increase in AST (SGOT) was 1.2 mU/mL and the mean decrease in ALT (SGPT) was 0.3 mU/mL. None of the individual AST or ALT values increased to 2 times the ULN.

During treatment with Lovastatin XL, the mean increases in creatine phosphokinase (CPK) from baseline to Week 3 and Week 4 were 7.9 mU/mL and 2.4 mU/mL, respectively. Mean increases of 7.1 mU/mL and 9.6 mU/mL were noted during treatment with Mevacor from baseline to Week 3 and Week 4, respectively. None of the individual CPK values increased to 2 times the ULN.

The mean and median chemistry laboratory values at baseline and during the active treatment periods were comparable for Lovastatin XL and Mevacor. Examination of individual serum constituents indicates relatively minor treatment-associated changes in each treatment arm. In addition, the changes observed during the Lovastatin XL treatment period were similar to those observed with Mevacor.

There were no clinically significant changes in physical examinations or vital signs reported during the study.

Conclusions: The pharmacokinetic data indicate that after administration of Lovastatin XL, the plasma concentrations of lovastatin prodrug are higher than those observed with Mevacor. Compared to Mevacor at steady state, administration of Lovastatin XL is associated with lower C_{max} and similar bioavailability of the active drug and HMG-CoA reductase inhibitors. The risk of myositis with statins is considered to be related to the concentration of active drug and/or metabolites in the systemic circulation.[1,2] Compared to Mevacor, at equivalent doses, Lovastatin XL demonstrated increased efficacy despite similar bioavailability of the active drug as well as the total and active inhibitors of HMG-CoA reductase. Thus, for a given level of LDL-C reduction with Lovastatin XL, there would be relatively lower concentrations of active drug and/or metabolites in the systemic circulation. This would translate into a "dose-sparing effect" and a resulting safety advantage.

Date of report: December 30, 1999

Reference(s):

1. Christians U, Jacobsen W, Floren LC. Metabolism and Drug Interactions of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in Transplant Patients. Are the Statins Mechanistically Similar? *Pharmacol Therap* 1998;80:1-34.

2. Moghadasian MH. Clinical Pharmacology of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors. *Life Sci* 1999; 65(13):1329-37.

Study No. 146-007

Title of study: A Single-Dose Safety and Pharmacokinetic Study of Lovastatin XL 10, 20 and 40 mg in Healthy Male Subjects

Investigator:

Study site: One study center in the United States

Publications (references): none

Studied period (days): 17 days **Phase of development:** I
Initiation date (first patient visit): 09-May-98
Completion date (last patient completed): 25-May-98

Objective: The objective of this study was to determine the safety and pharmacokinetic profiles of lovastatin and its β-hydroxyacid (lovastatin acid) for Lovastatin XL 10 and 20 mg formulations relative to the 40 mg formulation.

Methodology: This was a single-center, single-dose, open-label, randomized, three-period crossover study with a 7 day washout period between the treatments. Subjects were randomized to receive a single dose of three separate drug administrations in the assigned study periods, which consisted of one of the following: one Lovastatin XL 10 mg tablet, one Lovastatin XL 20 mg tablet, or one Lovastatin XL 40 mg tablet. All subjects were served dinner at approximately 5:30 p.m. followed by dosing at approximately 10:00 p.m.

Number of subjects (planned and analyzed): Nine (9) healthy, male subjects were planned and enrolled. Eight (8) subjects completed the study and were included in the data analysis. One subject discontinued from the study after the first treatment (Lovastatin XL 10 mg) due to personal reasons.

Diagnosis and main criteria for inclusion: Healthy, non-smoking, male subjects between the ages of 18 and 45 years.

Test product, dose/strength/concentration and mode of administration, lot number(s): Subjects received one of the following three separate drug administrations in each assigned study period: one Lovastatin XL 10 mg tablet (Lot No. P98185), one Lovastatin XL 20 mg tablet (Lot No. P98186), or one Lovastatin XL 40 mg tablet (Lot No. P97263).

Reference therapy, dose and mode of administration, lot number(s): There was no reference therapy for this study.

Duration of treatment: Single dose x 3

Criteria for evaluation:

Efficacy: This was not an efficacy study.

Pharmacokinetic/Pharmacodynamic: The following pharmacokinetic parameters were determined for plasma lovastatin and lovastatin acid: AUC_{0-48hr} (the area under the plasma concentration-time curve); C_{max} (the observed maximum concentration); T_{max} (the observed time to reach the maximum concentration); and T_{lag} (lag time). Geometric mean ratios were calculated for C_{max} and AUC_{0-48hr}, and average dose-normalized values were calculated for C_{max} (NC_{max}) and AUC (NAUC) for lovastatin and lovastatin acid.

Safety: Safety was evaluated by assessing the occurrence and frequency of adverse events, changes in vital signs, physical examinations, electrocardiograms (EKGs) and clinical laboratory values.

Data analysis methods: Plasma [illegible] for lovastatin and its β-hydroxyacid were analyzed at [illegible] using a pre-validated [illegible] method. Statistical analyses were performed on dose-normalized AUC_{0-48hr} (NAUC) and C_{max} (NC_{max}) for lovastatin and lovastatin acid. A crossover model, which included period, treatment, and carryover as the within-subject variables, was used to analyze the data. The level of significance for carryover effect was set at α=0.10. All other tests were performed at α=0.05. Dose-proportionality with the range of study doses would be declared if no significant differences between doses were observed with respect to NAUC and NC_{max}.

Summary/Conclusions:

Efficacy results: Not applicable

Pharmacokinetic Results: The mean ± SD pharmacokinetic data from the 8 completed subjects are summarized in the following table:

Table 1. Mean ± SD Values of Lovastatin and Lovastatin Acid

Lovastatin

Parameter	10 mg	20 mg	40 mg
C_{max} (ng/mL)	1.04 ± 0.43	2.03 ± 0.65	4.09 ± 3.02
AUC_{0-48hr} (ng•hr/mL)	14.6 ± 7.8	34.1 ± 13.7	53.9 ± 35.6
T_{lag} (hr)	5.2 ± 3.2	3.6 ± 1.3	1.9 ± 0.9
T_{max} (hr)	12.8 ± 2.1	13.5 ± 2.8	14.3 ± 4.5

Source: Final Study Report

Lovastatin Acid

Parameter	10 mg	20 mg	40 mg
C_{max} (ng/mL)	1.13 ± 1.03	2.14 ± 1.48	3.85 ± 2.66
AUC_{0-48hr} (ng•hr/mL)	19.2 ± 15.3	38.5 ± 25.6	71.3 ± 61.3
T_{lag} (hr)	3.4 ± 1.5	3.5 ± 1.2	2.5 ± 0.8
T_{max} (hr)	16.0 ± 9.1	17.3 ± 8.5	13.0 ± 7.7

Source: Final Study Report

Table 2. Geometric Mean Ratios for Lovastatin and Lovastatin Acid

Lovastatin			
Parameter	40 mg/20 mg	40 mg/10 mg	20 mg/10 mg
C_{max}	1.65	3.37	2.04
$AUC_{0-\infty}$	1.37	3.66	2.69
Lovastatin Acid			
Parameter	40 mg/20 mg	40 mg/10 mg	20 mg/10 mg
C_{max}	1.74	3.83	2.20
$AUC_{0-\infty}$	1.63	3.81	2.33

Source: Final Study Report

Table 3. Average Dose-Normalized Values for C_{max} (NC_{max}) and AUC (NAUC) for Lovastatin and Lovastatin Acid

Lovastatin			
Parameter	10 mg	20 mg	40 mg
NC_{max} (ng/mL)	0.80 ± 0.04	0.90 ± 0.03	0.10 ± 0.06
NAUC (ng•hr/mL)	1.45 ± 0.77	1.67 ± 0.67	1.39 ± 0.91
Lovastatin Acid			
Parameter	10 mg	20 mg	40 mg
NC_{max} (ng/mL)	0.11 ± 0.10	0.11 ± 0.07	0.10 ± 0.07
NAUC (ng•hr/mL)	1.90 ± 1.52	1.89 ± 1.26	1.83 ± 1.56

Source: Final Study Report

The pharmacokinetic results demonstrated that 10- and 20-mg doses of Lovastatin XL had similar profiles to the 40-mg dose of Lovastatin XL, showing delayed- and extended-release characteristics *in-vivo* in terms of plasma concentrations of lovastatin and lovastatin acid. In addition, 16 of 24 time-concentration profiles for lovastatin and 13 of 24 time-concentration profiles for lovastatin acid had non-quantifiable plasma concentrations at the 48-hour sampling time indicating that sampling for 48 hours was sufficient to characterize the pharmacokinetic profiles of lovastatin at the doses tested.

The mean dose-normalized values for C_{max} and $AUC_{0-\infty}$ would suggest dose proportionality for doses of Lovastatin XL 10, 20, and 40 mg. However, the observed carryover effect made a critical difference in the assessment of dose proportionality for this study. As predose and early samples for each dose of lovastatin were non-quantifiable, the concentration data provide no clear evidence for carryover with respect to plasma concentrations of lovastatin and lovastatin acid. Given the large variability in pharmacokinetic parameters due to the low bioavailability of Lovastatin XL formulations, it appears likely that the observed statistically significant carryover effect might be due to the sample size of 8, which resulted in only 2-3 subjects for each treatment sequence. However, as it is not possible to reliably determine if carryover effects were in fact real or were an artifact due to the small sample sizes, a larger sample size would be needed to provide a definitive assessment of dose-proportionality for Lovastatin XL dosages of 10, 20, and 40 mg.

Safety results: The safety profiles from this study with respect to adverse events and clinical laboratory tests indicated that single doses of Lovastatin XL 10, 20, and 40 mg were well tolerated by all participants. In addition, there were no clinically significant changes in physical examinations, EKGs, or vital signs reported during the study.

Conclusions: Single doses of Lovastatin XL 10, 20, and 40 mg were generally well tolerated by all participants in terms of adverse events and clinical laboratory tests. The pharmacokinetic profiles of lovastatin and lovastatin acid exhibited delayed- and extended-release characteristics *in vivo* for each dose. Mean dose-normalized values for C_{max} and $AUC_{0-\infty}$ suggested dose proportionality for doses of 10, 20, and 40 mg of Lovastatin XL. However, the small sample size and the presence of statistically significant carryover effects did not permit a definitive statement regarding dose-proportionality based on the current study.

Date of report: April 19, 2000

Study No. 146-012

Title of study: A Dose Proportionality Study of Lovastatin XL in the Dosage Levels of 20, 40, and 60 mg after Single Oral Dose to Healthy Subjects

Investigator: [redacted]

Study site: One study center in the United States

Publications (references): none

Studied period (days): 42 days
Phase of development: I
Initiation date (first patient visit): 26-Oct-99
Completion date (last patient completed): 06-Dec-99

Objective: The objectives of this study were 1) to determine the kinetic linearity of Lovastatin XL in the dosage levels of 20, 40 and 60 mg in healthy adult subjects in terms of plasma concentrations of lovastatin and lovastatin acid; 2) to characterize the disposition of Lovastatin XL by determining urinary excretion of lovastatin and lovastatin acid; and 3) to evaluate the effects of gender on pharmacokinetics of Lovastatin XL.

Methodology: This was a single-center, single-dose, open-label, randomized, three-period, six-sequence crossover study with a 2-week washout period between the treatments. Subjects were randomized to receive a single dose of three separate drug administrations in the assigned study periods, which consisted of one of the following: one Lovastatin XL 20 mg tablet; one Lovastatin XL 40 mg tablet; and one Lovastatin XL 20 mg tablet plus one Lovastatin XL 40 mg tablet. All subjects were served dinner at approximately 5:30 p.m. followed by dosing at approximately 10:00 p.m.

Number of subjects (planned and analyzed): Twenty-four (12 males and 12 females) healthy subjects were enrolled. Twenty-two (12 males and 10 females) completed the study. One female subject (Subject 19) was discontinued from the study after the first treatment due to taking prescription medications during the washout between period I and period II. Another female subject (Subject 23) was withdrawn from the study prior to the third dose because of positive testing for opiates at check-in for Period III.

Diagnosis and main criteria for inclusion: Healthy male and female subjects between the ages of 19 and 45 years who met all of the inclusion (and none of the exclusion) criteria.

Test product, dose/strength/concentration and mode of administration, lot number(s): Subjects received one of the following three separate drug administrations in each assigned study period: one Lovastatin XL 20 mg tablet (Lot No. 770R002), one Lovastatin XL 40 mg tablet (Lot No. 780R005), or one Lovastatin XL 20 mg tablet (Lot No. 770R002) plus one Lovastatin XL 40 mg tablet (Lot No. 780R005). All subjects were served dinner at approximately 5:30 p.m. followed by dosing at approximately 10:00 p.m.

Reference therapy, dose and mode of administration, lot number(s): There was no reference therapy for this study.

Duration of treatment: Single dose x 3

Criteria for evaluation:

Efficacy: This was not an efficacy study.

Pharmacokinetic/Pharmacodynamic: The following pharmacokinetic parameters were determined for plasma lovastatin and lovastatin acid: AUC_{0-72h} (the area under the plasma concentration-time curve); AUC_{0-72h}/BW (body weight normalized area under the plasma concentration-time curve); C_{max} (the observed maximum concentration); C_{max}/BW (body weight normalized observed maximum concentration); T_{max} (the observed time to reach the maximum concentration); and T_{lag} (lag time). Body weight and dose normalized mean values were calculated for C_{max} (NC_{max}) and AUC_{0-72h} ($NAUC_{0-72h}$) for lovastatin and lovastatin acid.

Safety: Safety was evaluated by assessing the occurrence and frequency of adverse events, changes in vital signs, physical examinations, electrocardiograms (EKGs) and clinical laboratory values.

Data analysis methods: Plasma lovastatin and its lovastatin acid were characterized in terms of AUC_{0-72h}, AUC_{0-72h}/BW, C_{max}, C_{max}/BW, T_{max}, T_{lag}, NC_{max}, and $NAUC_{0-72h}$.

A full model which included gender, sequence and gender-by-sequence terms as between-subject effects and period, period-by-gender, dose, dose-by-gender, carryover and carryover-by-gender as within-subject effects, was first used to examine the gender effect and to check whether data for both genders could be pooled together. If a significant ($p \leq 0.10$) interaction between gender and any within-subject main effect (period or dose or carryover) was observed, the data was evaluated separately for each gender.

To assess dose proportionality, body weight and dose normalized C_{max} (NC_{max}) and AUC_{0-72h} ($NAUC_{0-72h}$) were analyzed with a crossover model, which included sequence, period, dose and carryover terms for each gender. When no evidence of carryover effect ($p > 0.10$) was found, a reduced model with carryover effect dropped from the model was used to analyze the data. Comparisons between doses were made. Deviation from dose-linearity was indicated by significant differences ($p \leq 0.05$) between doses.

Safety observations and measurements as well as adverse events data were summarized. No formal statistical evaluation was applied to the safety variables; however, a clinical interpretation was performed.

Summary/Conclusions:

Efficacy results: Not applicable

Pharmacokinetic Results: The mean ± SD pharmacokinetic data of lovastatin and lovastatin acid in male (n=12) and female (n=10) subjects are summarized below:

Table 1. Mean ± SD Values of Lovastatin

Lovastatin			
Parameter	20 mg	40 mg	60 mg
C_{max} (ng/mL)			
Males	1.70 ± 1.07	3.45 ± 1.94	5.62 ± 4.33
Females	1.17 ± 0.80	2.65 ± 1.39	3.24 ± 1.59
C_{max}/BW (ng/mL•kg)			
Males	0.022 ± 0.012	0.046 ± 0.024	0.074 ± 0.058
Females	0.019 ± 0.013	0.043 ± 0.020	0.054 ± 0.029
AUC_{0-72hr} (ng•hr/mL)			
Males	33.5 ± 19.9	64.8 ± 35.7	116.3 ± 70.6
Females	20.1 ± 10.2	44.0 ± 17.9	70.7 ± 32.6
AUC_{0-72hr}/BW (ng•hr/mL•kg)			
Males	0.429 ± 0.214	0.856 ± 0.445	1.526 ± 0.898
Females	0.326 ± 0.169	0.783 ± 0.300	1.167 ± 0.603
T_{lag} (hr)			
Males	3.1 ± 0.8	3.6 ± 1.5	3.2 ± 0.9
Females	4.1 ± 1.1	3.6 ± 1.1	4.0 ± 1.2
T_{max} (hr)			
Males	14.0 ± 7.0	13.2 ± 2.5	16.3 ± 9.4
Females	11.4 ± 2.1	12.4 ± 4.4	11.4 ± 2.7

Source: Final Study Report

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Table 2. Mean ± SD Values of Lovastatin Acid

Lovastatin Acid			
Parameter	20 mg	40 mg	60 mg
C_{max} (ng/mL)			
Males	1.53 ± 0.85	3.41 ± 2.93	4.09 ± 2.29
Females	1.84 ± 1.16	3.57 ± 2.85	5.90 ± 4.22
C_{max}/BW (ng/mL•kg)			
Males	0.021 ± 0.013	0.048 ± 0.048	0.055 ± 0.034
Females	0.030 ± 0.018	0.060 ± 0.053	0.097 ± 0.072
AUC_{0-72hr} (ng•hr/mL)			
Males	36.1 ± 21.3	68.3 ± 34.5	114.3 ± 72.5
Females	34.7 ± 31.0	68.0 ± 48.5	110.9 ± 79.8
AUC_{0-72hr}/BW (ng•hr/mL•kg)			
Males	0.487 ± 0.311	0.938 ± 0.571	1.554 ± 1.066
Females	0.553 ± 0.441	1.121 ± 0.872	1.800 ± 1.254
T_{lag} (hr)			
Males	3.1 ± 0.8	3.7 ± 1.6	3.2 ± 0.9
Females	4.0 ± 0.8	3.7 ± 1.3	3.5 ± 1.4
T_{max} (hr)			
Males	11.5 ± 3.3	12.5 ± 2.7	17.7 ± 9.5
Females	9.4 ± 2.8	11.2 ± 2.5	12.6 ± 6.6

Source: Final Study Report

Body weight and dose normalized mean C_{max} (NC_{max}) and AUC_{0-72h} ($NAUC_{0-72h}$) values of lovastatin and lovastatin acid are summarized below:

Table 3. Body Weight and Dose Normalized Mean ± SD Values of Lovastatin

Lovastatin			
Parameter	20 mg	40 mg	60 mg
NC_{max} (ng/mL•kg•mg)			
Males	0.0011 ± 0.0006	0.0011 ± 0.0006	0.0012 ± 0.0010
Females	0.0010 ± 0.0007	0.0011 ± 0.0005	0.0009 ± 0.0005
$NAUC_{0-72h}$ (ng•hr/mL•kg•mg)			
Males	0.0215 ± 0.0107	0.0214 ± 0.0111	0.0254 ± 0.0150
Females	0.0163 ± 0.0084	0.0196 ± 0.0075	0.0195 ± 0.0101

Source: Final Study Report

Table 4. Body Weight and Dose Normalized Mean ± SD Values of Lovastatin Acid

Lovastatin Acid			
Parameter	20 mg	40 mg	60 mg
NC_{max} (ng/mL•kg•mg)			
Males	0.0010 ± 0.0006	0.0012 ± 0.0012	0.0009 ± 0.0006
Females	0.0015 ± 0.0009	0.0015 ± 0.0013	0.0016 ± 0.0012
$NAUC_{0-72h}$ (ng•hr/mL•kg•mg)			
Males	0.0244 ± 0.0156	0.0234 ± 0.0143	0.0259 ± 0.0178
Females	0.0277 ± 0.0220	0.0280 ± 0.0218	0.0300 ± 0.0259

Source: Final Study Report

Safety results: All participating subjects generally tolerated the study medications well. There were no clinically significant changes in physical examination, EKGs, vital signs, adverse events, and clinical safety laboratory measurements over the course of the study. The major adverse experiences reported from several subjects after administration of study medication were headache, abdominal pain, postural hypotension, anorexia, dyspepsia and rhinitis. The adverse experiences were either mild or moderate with a short duration and did not show a trend with the increase of dose.

Conclusions: Single doses of Lovastatin XL 20, 40, and 60 mg were generally well tolerated by all participants in terms of adverse events and clinical laboratory tests.

The pharmacokinetic profiles of lovastatin and lovastatin acid exhibited delayed- and extended-release characteristics for each dose level of Lovastatin XL. The mean values of plasma peak (C_{max}) and area under the plasma concentration-time curve (AUC_{0-72h}) of lovastatin, but not lovastatin acid, in male subjects were higher than those in female subjects. However, the difference was not statistically significant, indicating that gender did not affect the pharmacokinetics of Lovastatin XL.

Since gender interactions with period, dose or carryover for the key pharmacokinetic parameters (NC_{max} and $NAUC_{0-72h}$) of lovastatin and lovastatin acid existed, the dose proportionality was evaluated for male and female subjects separately.

Body weight and dose normalized values for C_{max} (NC_{max}) and AUC_{0-72h} ($NAUC_{0-72h}$) values of lovastatin and lovastatin acid were comparable across the three doses in both genders. No statistically significant differences for these parameters were found, indicating dose proportionality in the dosage levels of Lovastatin XL 20, 40, and 60 mg in both males and female subjects.

The amount of lovastatin and lovastatin acid excreted in urine after administration of Lovastatin XL was negligible since the concentrations of lovastatin and lovastatin acid in all urine samples collected were below the lower limit of quantitation of the assay.

Date of report: July 27, 2000

Study No. 146-102

Title of study: A Bioavailability Study of Lovastatin XL 60 mg Given By One Tablet (60 mg) Relative to Lovastatin XL 60 mg Given By Two Tablets (20 mg + 40 mg) After Single Oral Dose To Healthy Subjects

Investigator: [redacted]

Study site: One study center in the United States

Publications (references): none

Studied period (days): 37 days **Phase of development:** 1
Initiation date (first patient visit): 02-Nov-00
Completion date (last patient completed): 08-Dec-00

Objective: The objective of this study was to compare the bioavailability of Lovastatin XL 60 mg given by one tablet (one 60 mg tablet) with Lovastatin XL 60 mg given by two tablets (one 20 mg tablet + one 40 mg tablet) in healthy male subjects in terms of plasma concentrations of lovastatin and lovastatin acid.

Methodology: This was a single-center, open-label, single-dose, randomized, two-period crossover study with a two-week washout period between the treatments. The subjects randomly received a single oral dose of two separate drug administrations in assigned study periods, which consisted of one of the following treatments:

Treatment A = Lovastatin XL 60 mg (one 60 mg tablet)

Treatment B = Lovastatin XL 60 mg (one 20 mg tablet + one 40 mg tablet)

On the dosing day of each period, all subjects were served dinner at approximately 5:30 p.m., followed by dosing at approximately 10:00 p.m., one-half hour before bedtime.

Number of subjects (planned and analyzed): Twenty-four (24) subjects enrolled and 24 completed the study.

Diagnosis and main criteria for inclusion: Healthy male subjects 19 to 45 years of age.

Test product, dose/strength/concentration and mode of administration, lot number(s): Depending on the period and assigned treatment, subjects were instructed to take either one Lovastatin XL 60 mg tablet (Lot No. 790R001), or one Lovastatin XL 20 mg tablet (Lot No. 770R002) and one Lovastatin XL 40 mg tablet (Lot No. 780R005) at approximately 10:00 p.m., one-half hour before bedtime.

Reference therapy, dose and mode of administration, lot number(s): There was no reference therapy.

Duration of treatment: Single dose x 2

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Criteria for evaluation:

Efficacy: This was not an efficacy study.

Pharmacokinetic/Pharmacodynamic: The pharmacokinetic parameters [C_{max}, AUC_{0-72h}, $AUC_{0-\infty}$, T_{lag}, T_{max}, and $t_{1/2}$] were determined for lovastatin and lovastatin acid. The ratios of Lovastatin XL 60 mg/Lovastatin XL 20 mg + 40 mg for C_{max}, AUC_{0-72h} and $AUC_{0-\infty}$ were calculated.

Safety: Safety was evaluated by assessing the occurrence and frequency of adverse experiences, changes in vital signs, electrocardiograms (EKGs), physical examinations, and clinical laboratory values.

Data analysis methods: Summary statistics are presented for plasma concentrations of lovastatin and lovastatin acid at all timepoints by treatment. Summary statistics are also presented for plasma concentrations of lovastatin and lovastatin acid by treatment for the following pharmacokinetic parameters: C_{max}, AUC_{0-72h}, $AUC_{0-\infty}$, T_{max}, T_{lag}, and $t_{1/2}$. These parameters were estimated using a non-compartmental approach. The AUC and C_{max} values were compared between the two treatments. Relative bioavailability, which is defined as the ratio of AUC or C_{max} for the two treatments, was calculated and summarized.

A crossover model, which included sequence, subject-within-sequence, period, and treatment terms, was used to analyze natural log transformed AUC and C_{max} data. The estimates of treatment differences and their standard errors obtained from the crossover analysis were used to calculate the relative bioavailability and the 90% confidence interval. If the 90% confidence interval was within the interval [redacted], bioequivalence of the two treatments was declared.

Summary/Conclusions:

Efficacy results: Not applicable

Pharmacokinetic Results: The mean ± SD pharmacokinetic data from 24 subjects are summarized in the following tables for lovastatin and lovastatin acid:

Lovastatin

Parameter	Lovastatin XL 60 mg	Lovastatin XL 20 mg + 40 mg	Relative Bioavailability[a]	90% Confidence Interval
C_{max} (ng/mL)	4.94 ± 2.51	4.83 ± 1.61	107%	(93.4%, 117.4%)
AUC_{0-72h} (ng•hr/mL)	68.5 ± 33.6	66.4 ± 26.8	102%	(87.2%, 119.6%)
$AUC_{0-\infty}$ (ng•hr/mL)	72.2 ± 34.9	69.3 ± 33.1	103%	(89.0%, 124.6%)
T_{lag} (hr)	3.3 ± 1.3	3.0 ± 1.0	--	
T_{max} (hr)	14.1 ± 2.9	13.4 ± 2.5	--	
$t_{1/2}$ (hr)	4.8[b]	5.4[b]	--	

[a] Least square mean ratio of Lovastatin XL 60 mg/Lovastatin XL 20 mg + 40 mg
[b] Harmonic mean
Source: Final Study Report

Treatment with one 60 mg tablet of Lovastatin XL or one 20 mg tablet + one 40 mg tablet of Lovastatin XL resulted in similar pharmacokinetics of lovastatin.

Statistical data shown in the above table indicate that one 60 mg tablet of Lovastatin XL was bioequivalent to one 20 mg tablet + one 40 mg tablet of Lovastatin XL, in terms of the 90% confidence intervals for the least square mean ratios of C_{max}, AUC_{0-72hr} and AUC_{0-inf}

The pharmacokinetic parameters for lovastatin acid are displayed in the following table.

Lovastatin acid

Parameter	Lovastatin XL 60 mg	Lovastatin XL 20 mg + 40 mg	Relative bioavailability[a]	90% Confidence Interval
C_{max} (ng/mL)	4.16 ± 2.61	5.06 ± 5.04	93%	(82.2%, 104.5%)
AUC_{0-72hr} (ng•hr/mL)	72.9 ± 43.6	82.9 ± 70.5	94%	(83.8%, 106.5%)
AUC_{0-inf} (ng•hr/mL)	76.6 ± 46.3	82.1 ± 80.4	98%	(82.2%, 117.5%)
T_{lag} (hr)	3.5 ± 1.0	3.2 ± 0.9	–	
T_{max} (hr)	14.3 ± 3.9	12.7 ± 4.6	–	
$t_{1/2}$ (hr)	6.0[b]	5.7[b]	–	

[a] Least square mean ratio of Lovastatin XL 60 mg/Lovastatin XL 20 mg + 40 mg
[b] Harmonic mean
Source: Final Study Report

Treatment with one 60 mg tablet of Lovastatin XL or one 20 mg tablet + one 40 mg tablet of Lovastatin XL resulted in similar pharmacokinetics of lovastatin acid.

Statistical data shown in the above table indicate that one 60 mg tablet of Lovastatin XL was bioequivalent to one 20 mg tablet + one 40 mg tablet of Lovastatin XL, in terms of the 90% confidence intervals for the least square mean ratios of C_{max}, AUC_{0-72hr} and AUC_{0-inf}

Safety results: Overall, 2 (8.3%) subjects treated with one 60 mg tablet of Lovastatin XL and 2 (8.3%) subjects treated with one 20 mg tablet + one 40 mg tablet of Lovastatin XL experienced at least one TESS (treatment-emergent signs and symptoms) during the study. Specific TESS included headache (1 subject treated with one 60 mg tablet and 1 subject treated with one 20 mg tablet + one 40 mg tablet), mouth ulceration (1 subject treated with one 20 mg tablet + one 40 mg tablet), nausea and vomiting (1 subject treated with one 20 mg tablet + one 40 mg tablet), pharyngitis and rhinitis (1 subject treated with one 60 mg tablet).

One of the TESS (headache experienced by Subject 13 while treated with one 20 mg tablet + one 40 mg tablet) was considered by the investigator to be moderate in intensity. All other TESS were considered by the investigators to be mild in intensity. None of the TESS constituted an SAE, and none of the TESS resulted in the premature discontinuation of any subject from the study. Three of the TESS (headache, nausea, and vomiting experienced by Subject 13 while treated with one 20 mg tablet + one 40 mg tablet) were considered by the investigator to be possibly related to study medication. All other TESS were considered by the investigators not to be related to study medication.

Examination of individual serum chemistry parameters indicates relatively minor treatment-associated changes during each treatment arm. For all chemistry parameters, the changes observed during the Lovastatin XL 60 mg tablet treatment are similar to those with the Lovastatin XL one 20 mg tablet + one 40 mg tablet treatment. For both the Lovastatin XL 60 mg treatment periods, there were reductions of ~50 U/L in mean CPK from baseline to endpoint. These reductions in CPK were not considered to be clinically meaningful.

The results of the hematological analyses show no clinically meaningful changes for subjects receiving one 60 mg tablet of Lovastatin XL or one 20 mg tablet + one 40 mg tablet of Lovastatin XL.

There were no clinically significant changes observed in physical examinations and vital signs (blood pressure, pulse, and body temperature) during the study. In addition, there were no subjects with clinically significant EKG abnormalities.

Conclusions: Lovastatin XL taken as one 60 mg tablet was bioequivalent to Lovastatin XL administered as one 20 mg tablet + one 40 mg tablet on the basis of the lovastatin C_{max}, AUC_{0-72hr}, and AUC_{0-inf} being within the defined criteria for bioequivalency. Bioequivalency was also established for all 3 parameters (C_{max}, AUC_{0-72hr}, and AUC_{0-inf}) for lovastatin acid. The data demonstrated a similar T_{lag} and T_{max} for treatment with one 60 mg tablet of Lovastatin XL compared with one 20 mg tablet + one 40 mg tablet of Lovastatin XL. Lovastatin XL, taken either as a single 60 mg tablet or as one 20 mg tablet + one 40 mg tablet, was generally well tolerated by all participants in terms of adverse experiences and clinical laboratory tests.

Date of report: January 26, 2001

Study No. 146-103

Title of study: A Bioavailability Study of Lovastatin XL 40 mg Tablet (Final Marketing Image Product) Relative to MEVACOR® 40 mg Tablet After Single Oral Dose To Healthy Subjects

Investigator: _____

Study site: One study center in the United States

Publications (references): none

Studied period (days): 35 days **Phase of development:** I
Initiation date (first patient visit): 10-Oct-00
Completion date (last patient completed): 13-Nov-00

Objective: The objective of this study was to determine the bioavailability of the final marketing image of Lovastatin XL (40 mg tablet) relative to Mevacor (40 mg tablet) in healthy male subjects in terms of plasma concentrations of lovastatin and lovastatin acid.

Methodology: This was a single-center, open-label, single-dose, randomized, two-period crossover design with a two-week washout period between the treatments. The subjects randomly received a single oral dose of two separate drug administrations in assigned study periods, which consisted of one of the following:

Treatment A = Lovastatin XL 40 mg (one Lovastatin XL 40 mg tablet).

Treatment B = Mevacor 40 mg (one Mevacor 40 mg tablet).

In each study period, both study medications were administered at approximately 8:00 a.m. after an overnight fast.

Number of subjects (planned and analyzed): Twenty-four (24) subjects enrolled and 24 completed the study.

Diagnosis and main criteria for inclusion: Healthy male subjects 18 to 45 years of age.

Test product, dose/strength/concentration and mode of administration, lot number(s): Subjects were instructed to take one Lovastatin XL 40 mg (Lot No. 780R005) tablet at approximately 8:00 a.m. after an overnight fast.

Reference therapy, dose and mode of administration, lot number(s): Subjects were instructed to take one Mevacor 40 mg (Lot No. K0625) tablet at approximately 8:00 a.m. after an overnight fast.

Duration of treatment: Single dose x 2

Criteria for evaluation:

Efficacy: This was not an efficacy study.

Pharmacokinetic/Pharmacodynamic: The pharmacokinetic parameters [C_{max}, AUC_{0-48hr}, AUC_{0-inf}, T_{up}, T_{max}, and $t_{1/2}$] were determined for lovastatin and lovastatin acid. The ratios of Lovastatin XL/Mevacor for C_{max}, AUC_{0-48hr} and AUC_{0-inf} were calculated.

Safety: Safety was evaluated by assessing the occurrence and frequency of adverse experiences, changes in vital signs, electrocardiograms (EKGs), physical examinations, and clinical laboratory values.

Data analysis methods: Summary statistics are presented for plasma concentrations of lovastatin and lovastatin acid at all timepoints by treatment. Summary statistics are also presented for plasma concentrations of lovastatin and lovastatin acid by treatment for the following pharmacokinetic parameters: C_{max}, AUC_{0-48hr}, AUC_{0-inf}, T_{max}, T_{up}, and $t_{1/2}$. These parameters were estimated using a non-compartmental approach. The AUC and C_{max} were compared between the two treatments. Relative bioavailability, which is defined as the ratio of AUC or C_{max} for the two treatments, was calculated and summarized.

A crossover model, which included sequence, subject-within-sequence, period, and treatment terms, was used to analyze log-transformed AUC and C_{max} data. The estimates of treatment differences and their standard errors obtained from the crossover analysis were used to calculate the relative bioavailability and the 90% confidence interval. If the 90% confidence interval was contained in the interval _____, bioequivalence of the two treatments was declared.

Summary/Conclusions:

Efficacy results: Not applicable

Pharmacokinetic Results: The mean ± SD pharmacokinetic data from 24 subjects are summarized in the following tables for lovastatin and lovastatin acid:

Lovastatin

Parameter	Lovastatin XL	Mevacor	Geometric Mean Ratio[a]
C_{max} (ng/mL)	3.39 ± 1.39	2.80 ± 1.15	1.21
AUC_{0-48hr} (ng•hr/mL)	54.2 ± 20.4	37.6 ± 17.5	1.51
AUC_{0-inf} (ng•hr/mL)	63.5 ± 20.6	40.9 ± 17.5	1.41
T_{up} (hr)	2.5 ± 0.6	0.1 ± 0.2	--
T_{max} (hr)	10.4 ± 7.8	5.1 ± 2.2	--
$t_{1/2}$ (hr)	6.1[b]	6.9[b]	--

[a] Ratio = Lovastatin XL/Mevacor
[b] Harmonic mean
Source: Final Study Report

Lovastatin acid

Parameter	Lovastatin XL	Mevacor	Geometric Mean Ratio[a]
C_{max} (ng/mL)	3.37 ± 1.91	3.75 ± 1.81	0.89
AUC_{0-48hr} (ng•hr/mL)	58.0 ± 20.0	44.4 ± 17.2	1.33
AUC_{0-inf} (ng•hr/mL)	66.8 ± 22.4	53.3 ± 13.7	1.42
T_{lag} (hr)	2.4 ± 1.0	0.3 ± 0.3	--
T_{max} (hr)	11.2 ± 5.1	5.6 ± 2.5	--
$t_{1/2}$ (hr)	6.6[b]	9.1[b]	--

[a] Ratio = Lovastatin XL/Mevacor
[b] Harmonic mean
Source: Final Study Report

Lovastatin XL exhibited extended-release characteristics as manifested by a prolonged T_{lag} and a delayed T_{max}, compared to Mevacor, for lovastatin. For plasma lovastatin levels, the mean T_{lag} and T_{max} for Lovastatin XL were 2.5 hours and 10.4 hours, respectively, compared to 0.1 hours and 5.1 hours for Mevacor. The mean C_{max} was higher for Lovastatin XL (3.39 ng/mL), compared with Mevacor (2.80 ng/mL). Compared with Mevacor, the relative bioavailability of Lovastatin XL as measured by AUC_{0-48hr} was 51% greater in terms of lovastatin concentration.

Similar to lovastatin data, Lovastatin XL exhibited extended-release characteristics as manifested by a prolonged T_{lag} and a delayed T_{max}, compared to Mevacor, for lovastatin acid. For plasma lovastatin acid levels, the mean T_{lag} and T_{max} for Lovastatin XL were 2.4 hours and 11.2 hours, respectively, compared to 0.3 hours and 5.6 hours for Mevacor. The mean C_{max} was higher for Mevacor (3.75 ng/mL) compared with Lovastatin XL (3.37 ng/mL). Compared with Mevacor, the relative bioavailability of Lovastatin XL as measured by AUC_{0-48hr} was 33% greater in terms of lovastatin acid concentration.

Safety results: Overall, 4 (16.7%) subjects treated with Lovastatin XL and 4 (16.7%) subjects treated with Mevacor experienced at least one treatment-emergent sign or symptom (TESS) during the study. All of these TESS were considered by the investigators to be mild in intensity. None of the TESS constituted a serious adverse experience, and none of the TESS resulted in the premature discontinuation of any subject from the study. Three of the TESS (pharyngitis and abdominal pain experienced by subjects treated with Lovastatin XL, and headache experienced by a subject treated with Mevacor) were considered by the investigators to be possibly related to study medication. All other TESS were considered by the investigators not to be related to study medication.

The mean and median chemistry laboratory values at baseline and during the active treatment periods were comparable for Lovastatin XL and Mevacor. With the exception of creatine phosphokinase (CPK), examination of individual serum chemistry parameters indicates relatively minor treatment-associated changes in each treatment arm. For both the Lovastatin XL and Mevacor treatment periods, there were large reductions (~130 U/L) in mean CPK from baseline to endpoint. These reductions in CPK were not considered to be clinically meaningful.

The results of the hematological analyses show no clinically meaningful changes for patients receiving Lovastatin XL or Mevacor.

There were no clinically significant changes observed in physical examinations and vital signs (blood pressure and pulse) during the study. In addition, there were no subjects with clinically significant EKG abnormalities.

Conclusions: Lovastatin XL exhibited delayed- and extended-release characteristics compared to Mevacor. This was characterized by a prolonged T_{lag} and a delayed T_{max} with Lovastatin XL administration, compared with Mevacor administration. The systemic bioavailability of lovastatin and lovastatin acid, as measured by the AUC_{0-48hr} and AUC_{0-inf}, was greater for Lovastatin XL than for Mevacor. This indicates that more drug was absorbed in the gastrointestinal tract from Lovastatin XL than from Mevacor. Single 40 mg doses of Lovastatin XL and Mevacor were generally well tolerated by all participants in terms of adverse experiences and clinical laboratory tests.

Date of report: December 30, 2000

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/s/

Sang Chung
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PHARMACOLOGIST

Hae-Young Ahn
12/20/01 04:52:54 PM
BIOPHARMACEUTICS

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MEMO

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

Date: 18-May-2001

NDA:	21-316	**Sponsor:**	Aura Labs, Inc
Brand Name:	———	**Priority Classification:**	S
Generic Name:	Lovastatin ER	**Indication(s):**	Hyperlipidemia
Drug Class:	Lipid Altering Agents	**Date of Submission:**	30-March-2001
Dosage Form:	10/20/40/60 mg Tablets	**Route of Admin.:**	Oral
Dosing Regimen:	10-60 mg q.d.	**Due Date of Review:**	26-September-2001
Division:	DPE-II	**Medical Division:**	DMEDP
Reviewer:	Sang M. Chung	**Team Leader:**	Hae-Young Ahn

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		
Bioavailability and Bioequivalence Studies	X		
Mass Balance Study		X	
BA Studies		X	
Absolute BA			
Relative BA			
BE Studies	X		
Average BE	X		
Population BE		X	
Individual BE		X	
Food-Drug Interaction	X		
Dissolution Tests (In Vitro-In Vivo Comparison Studies)		X	
Studies Using Human Biomaterials		X	
Plasma Protein Binding Studies			
Blood/Plasma Ratio			
Metabolism Studies Using Hepatocytes, Microsomes,etc			
In Vitro Drug Interaction Studies			
Human Pharmacokinetics Studies	X		
PK, and Initial Safety and Tolerability in Healthy Volunteers	X		
Single Dose	X		
Multiple Dose		X	
PK, and Initial Safety and Tolerability in Patient Volunteers	X		
Single Dose		X	
Multiple Dose	X		
Dose Proportionality	X		
Single Dose	X		
Multiple Dose		X	

Items included in NDA (CTD)	*Yes*	*No*	*Request*
PK in Population Subsets to Evaluate Effects of Intrinsic Factors	X		
Ethnicity		X	
Gender	X		
Pediatrics		X	
Geriatrics		X	
Renal Impairment		X	
Hepatic Impairment		X	
PK to Evaluate Effects of Extrinsic Factors		X	
Drug-Drug Interaction: Effects on Primary Drug		X	
Drug-Drug Interaction: Effects of Primary Drug		X	
Population PK studies		X	
Summary Table of PK/PD Studies		X	
PK/PD studies in Volunteers		X	
PK/PD studies in patients		X	
Individual Datasets for all PK and PK/PD studies in electronic format	X		
Other	X		
Genotype/Phenotype Studies		X	
Chronopharmacokinetics		X	
Literature	X		

Submission in Brief

Aura Lab., Inc has submitted this NDA for ——— a lovastatin extended-release tablets for indication of dyslipidemia and secondary prevention of coronary heart disease. The indications are based on Mevacor® labeling, the approved immediate-release product.

Nine human pharmacokinetic studies are included in this application:

- Eight studies for 1) dose proportionality, 2) relative bioavailability studies relative to Mevacor® as a reference product, 3) food effect on ——— and 4) dosage form equivalence in healthy volunteers and
- One multiple dose study in hypercholesterolemia volunteers

This application is filable.

QBR questions: (Key Issues to be Considered)

1. What are lovastatin and lovastatin acid pharmacokinetics from ——— compared to those from Mevacor® ?
2. Is there dose-dumping phenomenon ?
3. Is there food effect on ———

Sign/Date _____ _____

Sang M. Chung, Ph.D., Reviewer **Hae-Young Ahn, Ph.D., Team Leader**

CC: NDA 21-316 (orig, 1 copy), HFD-850(Lee), HFD-510(Simoneau), HFD-870(Ahn, Chung), HFD-850(Lesko), CDR.

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/s/

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PHARMACOLOGIST

Hae-Young Ahn
7/5/01 11:50:04 AM
BIOPHARMACEUTICS

Amendment of
Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-316
Brand Name:	Altocor™ Tablets
Generic Name:	Lovastatin extended-release tablets
Strength(s):	10, 20, 40, 60 mg
Sponsor:	Aura Laboratories, Inc. 401 Hackensack Ave. Hackensack, NJ 07601
Submission Date:	30-March-2001
Submission Type:	Original Application – Immediate release to Modified release
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Hae-Young Ahn, Ph.D.

Executive Summary

The sponsor submitted 505(b)2 application (NDA 21-316) of lovastatin, a cholesterol lowering agent. In the original application, the sponsor described that lovastatin release had extended as well as delayed characteristics from the formulation with significantly longer T_{max}, and lower C_{max} of lovastatin and lovastatin acid compared to those of Mevacor, immediate release product.

During a teleconference held on January 3, 2002, the sponsor wanted to remove description about [redacted] of the formulation because the product was formulated with enteric coating material [redacted] However, the rate of delivery is slower in acidic media.

The sponsor's claim was consistent with *in vitro* dissolution data. There was certain degree of lovastatin release in the simulated gastric fluid after 4 hours with the proposed dissolution method. Therefore, it was agreed that the sponsor would delete description of [redacted] of the formulation from the label because [redacted] is normally associated with products that are [redacted]

The teleconference lead amendment of Clinical Pharmacology and Biopharmaceutics Review in the following aspects:

1. Phase IV commitment to develop a dissolution method and specification for assuring delayed characteristics of the formulation is not required any more.

2. The following recommended dissolution method and specification should be required not as an interim basis.

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

Dissolution specification;

Time (hr)	Amount Dissolved (%)
2	
8	

3. release was recommended as a description of both extended and release characteristics in the label. The term should be replaced by 'extended' because the sponsor would remove ' from the label.

4. The formulation is composed of an enteric coating material. Therefore, it is recommended that drug-drug interaction study between Altocor and antacid to monitor clinical concerns of the role of enteric coating material in an altered pH environment. The sponsor agreed to do the interaction study to measure pharmacokinetics of Altocor and it should be a Phase IV commitment.

Therefore, sections of Phase IV Commitment and Reviewers Comments in Clinical Pharmacology and Biopharmaceutics Review are amended accordingly and should be changed as follows:

IPhase IV Commitment

The sponsor should conduct a drug interaction study comparing the pharmacokinetics of lovastatin and lovastatin acid with and without concomitant antacid.

Reviewers Comments

The following dissolution method and specification is recommended:

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

Dissolution specification;

Time (hr)	Amount Dissolved (%)
2	
8	

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Hae-Young Ahn
1/17/02 04:50:33 PM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-316
Submission Date(s):	18-February-2002
Brand Name	Altocor
Generic Name	Lovastatin ER
Reviewer	Sang M. Chung, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation 2 (DPE-2)
OND division	Metabolic and Endocrine (HFD-510)
Sponsor	Aura Laboratories, Inc.
Submission Type	**Amendment for dissolution method and specification**
Strength(s)	10 mg, 20 mg, 40 mg, and 60 mg
Indication	Lipid altering

EXECUTIVE SUMMARY

In the original NDA, the sponsor proposed the following dissolution method and specification:

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml — sodium lauryl sulfate (SLS) / sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification:

Time (hr)	Specification
—	—
2	—
8	—
16	—

The Division (DPE-2) requested justification of — concentration and the following dissolution condition and specification were recommended based on the provided data:

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml — sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification:

Time (hr)	Specification
2	
8	

In this amendment the sponsor provided more dissolution data and it is summarized as follows:

- Mean (range) amount dissolved in — SLS, pH 6.5 dissolution medium

Time (hr)	10 mg	20 mg	40 mg	60 mg
1	4	4	1	0
2	23	20	10	5
8	85	85	80	75
16	90	89	88	84

- Mean (range) amount dissolved of 60 mg in SLS, pH 6.5 dissolution medium

Time (hr)				
1	0	0	0	0
2	3	3	3	3
4	28	28	31	32
8	72	73	72	73
16	84	84	80	83

The sponsor proposed the following based on the above data:

For 10 mg and 20 mg,

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml — sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification:

Time (hr)	Specification
2	
8	
16	

For 40 mg and 60 mg,

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml — sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification:

Time (hr)	Specification
2	
8	
16	

The —— concentration of — was decided by the sponsor to provide a saturated solution of 10 times the expected lovastatin concentration in the medium. The two specifications proposed by the sponsor appear to be based on Level 1 of acceptance criteria, USP XV. However, the Agency routinely set the specification based on Level 2 of acceptance criteria to assure better product quality control.

Therefore, the Division recommends the following dissolution method and specification:

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml — sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification based on level 2, USP XV:

Time (hr)	Specification
2	—
8	—
16	—

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II has reviewed the amendment submitted on February 18, 2002 and recommends the following dissolution method and specification:

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml — sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification based on level 2, USP XV:

Time (hr)	Specification
2	—
8	—
16	—

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BIOPHARMACEUTICS

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AMENDMENT OF
CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-316
Submission Date(s):	02-MAY-2002
Brand Name	Altocor
Generic Name	Lovastatin ER
Reviewer	Sang M. Chung, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation 2 (DPE-2)
OND division	Metabolic and Endocrine (HFD-510)
Sponsor	Aura Laboratories, Inc.
Submission Type	**Amendment for dissolution method and specification** (N021316-N000 BZ)
Strength(s)	10 mg, 20 mg, 40 mg, and 60 mg
Indication	Lipid altering

EXECUTIVE SUMMARY

In the original NDA, the sponsor proposed the following dissolution method and specification:

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml — sodium lauryl sulfate (SLS) / sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification:

Time (hr)	Specification
—	—
2	—
8	—
16	—

The Division (DPE-2) requested justification of —— concentration and the following dissolution condition and specification were recommended based on the provided data:

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml —— , sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification:

Time (hr)	Specification
2	
8	

In the first amendment (19-FEB-2002, N000 AZ), the sponsor adjusted concentration to for a saturated solution of 10 times the expected lovastatin concentration in the medium. The proposed condition and specifications was as follows:

For 10 mg and 20 mg,

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification:

Time (hr)	Specification
2	
8	
16	

For 40 mg and 60 mg,

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification:

Time (hr)	Specification
2	
8	
16	

The specifications proposed by the sponsor appeared to be based on Level 1 of acceptance criteria, USP XV. However, the Division recommended the following dissolution method and specification based on Level 2 of acceptance criteria to assure better product quality control.

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C
- Specification based on level 2, USP XV:

Time (hr)	Specification
2	
8	
16	

In this amendment, the sponsor accepted the Division's recommendation with expansion of range on both 8 and 16-hour specification as follows:

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml — sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C

- Specification:

Time (hr)	Specification
2	—
8	—
16	—

The expansion on 16-hour specification was primarily for 60 mg strength in stability program, which was within 10% of the proposed limit.

Upon review of provided additional dissolution data, — expansion of range on 8-hour specification is acceptable. However, the expansion of range on 16-hour specification is not acceptable for assurance in product quality between batches.

Therefore, the Division recommends — expansion only on 8-hour specification as follows:

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml — sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C

- Specification:

Time (hr)	Specification
2	—
8	—
16	—

The Division's recommendation was conveyed to the sponsor through teleconference on 17-May-2002 and the sponsor accepted it.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II has reviewed the amendment submitted on May 02, 2002 and recommends the following dissolution method and specification:

- Dissolution condition: USP apparatus II (paddle) at 50 RPM, 900 ml — sodium lauryl sulfate/sodium phosphate buffer (0.01M), pH 6.5, at 37°C

- Specification based on level 2, USP XV:

Time (hr)	Specification
2	—
8	—
16	—

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/s/

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