CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

75-828

Generic Name: Lovastatin Tablets, USP

Sponsor: PurePac Pharmaceuticals, Co.

Approval Date: December 17, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
75-828

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APPLICATION NUMBER:

75-828

APPROVAL LETTER

ANDA 75-828

DEC 17 2001

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application dated March 29, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg.

Reference is also made to our tentative approval letter dated September 13, 2001, and to your amendments dated June 28, 2000; October 26 and November 13, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Mevacor® Tablets, 10 mg, 20 mg, and 40 mg, respectively, of Merck Research Laboratories). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all

proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 12/17/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-828

TENTATIVE APPROVAL LETTER(S)

ANDA 75-828

SEP 13 2001

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application dated March 29, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg.

Reference is also made to our tentative approval letter dated December 19, 2000, and to your amendment dated August 20, 2001.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug remains safe and effective for use as recommended in the submitted labeling. Therefore, the application remains **tentatively approved.** This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Mevacor Tablets of Merck Research Laboratories, is currently subject to a period of patent protection (U.S. Patent No. 4,231,938). Your application contains a Paragraph III Certification to the '938 patent under Section 505(j)(2) (A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of this patent. As noted in the current edition of the Agency's publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", the "Orange Book", this patent was scheduled to expire on June 15, 2001. However, Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) created Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). Section 505A

permits the sponsor of the RLD to obtain an additional six months of exclusivity if, in accord with the statute, the sponsor submits data previously requested by the Agency relating to the use of the drug in the pediatric population. The RLD holder has submitted data to support the use of lovastatin in a pediatric population. The Agency's Pediatric Exclusivity Board has determined that the data support the granting of 6-months of exclusivity to the RLD. Consequently, the awarding of this exclusivity will effectively lengthen the life of the '938 patent for an additional 6 months. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the additional exclusivity period granted to the RLD holder has expired; i.e., currently December 15, 2001.

Because the Agency is granting a tentative approval for this application, please amend the application at least 60 days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment serves to reactivate your application, and should be submitted even if none of these changes were made. It should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this

drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to December 15, 2001, you should amend your application accordingly.

At the time you submit any amendments, you should contact Michelle Dillahunt, R.Ph., Project Manager, at 301-827-5848, for further instructions.

Sincerely yours,

/S/

Gary Buehler 9/13/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-828

DEC 19 2000

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application dated March 29, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg.

Reference is also made to your amendments dated June 28, October 19, and November 15, 2000.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Mevacor Tablets of Merck Research Laboratories, is currently subject to a period of patent protection which expires on June 15, 2001 (U.S. Patent No. 4,231,938). Your application contains a Paragraph III Certification to the '938 patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of this patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the '938 patent has expired, i.e., currently June 15, 2001.

Because the Agency is granting a tentative approval for this application, please submit an amendment between 60 and 90 days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. An amendment should be submitted even if none of these changes were made. This submission should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to June 15, 2001, you should amend your application accordingly.

At the time you submit any amendments, you should contact Michelle Dillahunt, R.Ph., Project Manager, at 301-827-5848, for further instructions.

Sincerely yours,

/S/

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

12/19/00

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

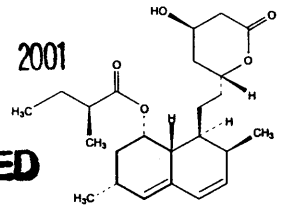
APPLICATION NUMBER:

75-828

APPROVED FINAL LABELING

DESCRIPTION:
Lovastatin is a cholesterol lowering agent isolated from a strain of *Aspergillus terreus*. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

Lovastatin is [1 *S*-[1α(*R**),3α,7β,8β(2*S**,4*S**), 8aβ]]-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The molecular formula of lovastatin is $C_{24}H_{36}O_5$ and its molecular weight is 404.55. Its structural formula is:



Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile.

Each tablet for oral administration, contains 10 mg, 20 mg, or 40 mg of lovastatin. In addition, each tablet contains the following inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. Butylated hydroxyanisole is added as a preservative. The 20 mg tablet also contains D&C Red #30 aluminum lake. The 40 mg tablet also contains D&C Yellow #10 HT aluminum lake.

40-8856

LOVASTATIN TABLETS, USP

Revised — November 2001

CLINICAL PHARMACOLOGY:
The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological and clinical studies have established that high LDL-C and low high-density lipoprotein cholesterol (HDL-C) are both associated with coronary heart disease. However, the risk of developing coronary heart disease is continuous and graded over the range of cholesterol levels and many coronary events do occur in patients with total cholesterol (total-C) and LDL-C in the lower end of this range.

Lovastatin has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very low-density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of lovastatin may involve both reduction of VLDL-C concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with lovastatin. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that lovastatin does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, lovastatin can produce increases of variable magnitude in HDL-C, and modestly reduces VLDL-C and plasma triglycerides (TG) (see Tables I-III under **Clinical Studies**). The effects of lovastatin on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

Lovastatin is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

Pharmacokinetics: Lovastatin is a lactone which is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of lovastatin.

Following an oral dose of ^{14}C-labeled lovastatin in man, 10% of the dose was excreted in urine and 83% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (lovastatin plus ^{14}C-metabolites) peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours post-dose. Absorption of lovastatin, estimated relative to an intravenous reference dose, in each of four animal species tested, averaged about 30% of an oral dose. In animal studies, after oral dosing, lovastatin had high selectivity for the liver, where it achieved substantially higher concentrations than in non-target tissues. Lovastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of lovastatin, the availability of drug to the general circulation is low and variable. In a single dose study in four hypercholesterolemic patients, it was estimated that less than 5% of an oral dose of lovastatin reaches the general circulation as active inhibitors. Following administration of lovastatin tablets the coefficient of variation, based on between-subject variability, was approximately 40% for the area under the curve (AUC) of total inhibitory activity in the general circulation.

Both lovastatin and its β-hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Animal studies demonstrated that lovastatin crosses the blood-brain and placental barriers.

The major active metabolites present in human plasma are the β-hydroxyacid of lovastatin, its 6'-hydroxy derivative, and two additional metabolites. Peak plasma concentrations of both active and total inhibitors were attained within 2 to 4 hours of dose administration. While the recommended therapeutic dose range is 10 to 80 mg/day, linearity of inhibitory activity in the general circulation was established by a single dose study employing lovastatin tablet dosages from 60 to as high as 120 mg. With a once-a-day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady state between the second and third days of therapy and were about 1.5 times those following a single dose. When lovastatin was given under fasting conditions, plasma concentrations of total inhibitors were on average about two-thirds those found when lovastatin was administered immediately after a standard test meal.

In a study of patients with severe renal insufficiency (creatinine clearance 10-30 mL/min), the plasma concentrations of total inhibitors after a single dose of lovastatin were approximately two-fold higher than those in healthy volunteers.

In a study including 16 elderly patients between 70-78 years of age who received lovastatin 80 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age (see **PRECAUTIONS, Geriatric Use**).

Lovastatin is a substrate for cytochrome P450 isoform 3A4 (CYP3A4) (see **PRECAUTIONS, Drug Interactions**). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study**, 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 80 mg lovastatin on the third day. This regimen of grapefruit juice resulted in a mean increase in the serum concentration of lovastatin and its β-hydroxyacid metabolite (as measured by the area under the concentration-time curve) of 15-fold and 5-fold, respectively [as measured using a chemical assay - high performance liquid chromatography]. In a second study, 15 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 40 mg lovastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using an enzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.34-fold and 1.36-fold, respectively, and of lovastatin and its β-hydroxyacid metabolite [measured using a chemical assay – liquid chromatography/tandem mass spectrometry - different from that used in the first** study] of 1.94-fold and 1.57-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied.

**Kantola, T, et al., Clin Pharmacol Ther 1998; 63(4): 397-402

Clinical Studies: Lovastatin has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of primary hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during continuation of therapy. Single daily doses given in the evening were more effective than the same dose given in the morning, perhaps because cholesterol is synthesized mainly at night.

In multicenter, double-blind studies in patients with familial or non-familial hypercholesterolemia, lovastatin, administered in doses ranging from 10 mg q.p.m. to 40 mg b.i.d., was compared to placebo. Lovastatin consistently and significantly decreased plasma total-C, LDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio. In addition, lovastatin produced increases of variable magnitude in HDL-C, and modestly decreased VLDL-C and plasma TG (see Tables I through III for dose response results).

The results of a study in patients with primary hypercholesterolemia are presented in Table I.

TABLE I
Lovastatin vs. Placebo
(Mean Percent Change from Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	TG.
Placebo	33	-2	-1	-1	0	+1	+9
Lovastatin							
10 mg q.p.m.	33	-16	-21	+5	-24	-19	-10
20 mg q.p.m.	33	-19	-27	+6	-30	-23	+9
10 mg b.i.d.	32	-19	-28	+8	-33	-25	-7
40 mg q.p.m.	33	-22	-31	+5	-33	-25	-8
20 mg b.i.d.	36	-24	-32	+2	-32	-24	-6

Lovastatin was compared to cholestyramine in a randomized open parallel study. The study was performed with patients with hypercholesterolemia who were at high risk of myocardial infarction. Summary results are presented in Table II.

TABLE II
Lovastatin vs. Cholestyramine
(Percent Change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TG. (mean)
Lovastatin								
20 mg b.i.d.	85	-27	-32	+9	-36	-31	-34	-21
40 mg b.i.d.	88	-34	-42	+8	-44	-37	-31	-27
Cholestyramine								
12 g b.i.d.	88	-17	-23	+8	-27	-21	+2	+11

Lovastatin was studied in controlled trials in hypercholesterolemic patients with well-controlled non-insulin dependent diabetes mellitus with normal renal function. The effect of lovastatin on lipids and lipoproteins and the safety profile of lovastatin were similar to that demonstrated in studies in nondiabetics. Lovastatin had no clinically important effect on glycemic control or on the dose requirement of oral hypoglycemic agents.

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Lovastatin was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2 mmol/L - 7.6 mmol/L], LDL-C >160 mg/dL [4.1 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. All changes in the lipid measurements (Table III) in lovastatin treated patients were dose-related and significantly different from placebo (p≤0.001). These results were sustained throughout the study.

TABLE III
Lovastatin vs. Placebo
(Percent Change from Baseline — Average Values Between Weeks 12 and 48)

DOSAGE	N**	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TG. (median)
Placebo	1663	+0.7	+0.4	+2.0	+0.2	+0.6	+4
Lovastatin							
20 mg q.p.m.	1642	-17	-24	+6.6	-27	-21	-10
40 mg q.p.m.	1645	-22	-30	+7.2	-34	-26	-14
20 mg b.i.d.	1646	-24	-34	+8.6	-38	-29	-16
40 mg b.i.d.	1649	-29	-40	+9.5	-44	-34	-19

**Patients enrolled

Atherosclerosis: In the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), the effect of therapy with lovastatin on coronary atherosclerosis was assessed by coronary angiography in hyperlipidemic patients. In the randomized, double-blind, controlled clinical trial, patients were treated with conventional measures (usually diet and 325 mg of aspirin every other day) and either lovastatin 20-80 mg daily or placebo. Angiograms were evaluated at baseline and at two years by computerized quantitative coronary angiography (QCA). Lovastatin significantly slowed the progression of lesions as measured by the mean change per-patient in minimum lumen diameter (the primary endpoint) and percent diameter stenosis, and decreased the proportions of patients categorized with disease progression (33% vs. 50%) and with new lesions (16% vs. 32%).

In a similarly designed trial, the Monitored Atherosclerosis Regression Study (MARS), patients were treated with diet and either lovastatin 80 mg daily or placebo. No statistically significant difference between lovastatin and placebo was seen for the primary endpoint (mean change per patient in percent diameter stenosis of all lesions), or for most secondary QCA endpoints. Visual assessment by angiographers who formed a consensus opinion of overall angiographic change (Global Change Score) was also a secondary endpoint. By this endpoint, significant slowing of disease was seen, with regression in 23% of patients treated with lovastatin compared to 11% of placebo patients.

In the Familial Atherosclerosis Treatment Study (FATS), either lovastatin or niacin in combination with a bile acid sequestrant for 2.5 years in hyperlipidemic subjects significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions by QCA compared to diet and, in some cases, low-dose resin.

The effect of lovastatin on the progression of atherosclerosis in the coronary arteries has been corroborated by similar findings in another vasculature. In the Asymptomatic Carotid Artery Progression Study (ACAPS), the effect of therapy with lovastatin on carotid atherosclerosis was assessed by B-mode ultrasonography in hyperlipidemic patients with early carotid lesions and without known coronary heart disease at baseline. In this double-blind, controlled clinical trial, 919 patients were randomized in a 2 x 2 factorial design to placebo, lovastatin 10-40 mg daily and/or warfarin. Ultrasonograms of the carotid walls were used to determine the change per patient from baseline to three years in mean maximum intimal-medial thickness (IMT) of 12 measured segments. There was a significant regression of carotid lesions in patients receiving lovastatin alone compared to those receiving placebo alone (p=0.001). The predictive value of changes in IMT for stroke has not yet been established. In the lovastatin group there was a significant reduction in the number of patients with major cardiovascular events relative to the placebo group (5 vs.14) and a significant reduction in all-cause mortality (1 vs. 8).

Eye: There was a high prevalence of baseline lenticular opacities in the patient population included in the early clinical trials with lovastatin. During these trials the appearance of new opacities was noted in both the lovastatin and placebo groups. There was no clinically significant change in visual acuity in the patients who had new opacities reported nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity.

A three-year, double-blind, placebo-controlled study in hypercholesterolemic patients to assess the effect of lovastatin on the human lens demonstrated that there were no clinically or statistically significant differences between the lovastatin and placebo groups in the incidence, type or progression of lenticular opacities. There are no controlled clinical data assessing the lens available for treatment beyond three years.

INDICATIONS AND USAGE:
Therapy with lovastatin should be a component of multiple risk factor intervention in those individuals with dyslipidemia at risk for atherosclerotic vascular disease. Lovastatin should be used in addition to a diet restricted in saturated fat and cholesterol as part of a treatment strategy to lower total-C and LDL-C to target levels when the response to diet and other nonpharmacological measures alone has been inadequate to reduce risk.

Coronary Heart Disease: Lovastatin is indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total-C and LDL-C to target levels.

Hypercholesterolemia: Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lovastatin tablets are indicated as an adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb***), when the response to diet restricted in saturated fat and cholesterol and to other non-pharmacological measures alone has been inadequate.

General Recommendations: Prior to initiating therapy with lovastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = total-C - [0.2 x TG + HDL-C]

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, lovastatin tablets are not indicated.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

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

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2 + Risk factors (10 year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-Lowering drug optional)

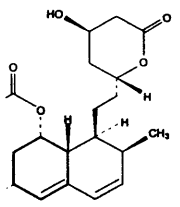
† CHD, coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

lowering agent isolated from a strain of
l ingestion, lovastatin, which is an inactive
corresponding β-hydroxyacid form. This is
n inhibitor of 3-hydroxy-3-methylglutaryl-
reductase. This enzyme catalyzes the
mevalonate, which is an early and rate
sis of cholesterol.

7),3α,7β,8β(2S*,4S*), 8aβ]]-1,2,3,7,8,8a-
2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-
methylbutanoate. The molecular formula of
molecular weight is 404.55. Its structural



nhygroscopic crystalline powder that is
ingly soluble in ethanol, methanol, and

stration, contains 10 mg, 20 mg, or 40 mg
ch tablet contains the following inactive
rate, magnesium stearate, microcrystalline
starch. Butylated hydroxyanisole is added
mg tablet also contains D&C Red #30
tablet also contains D&C Yellow #10 HT

OGY:

nsity lipoprotein cholesterol (LDL-C) in
l-documented in clinical and pathological
animal experiments. Epidemiological and
ed that high LDL-C and low high-density
C) are both associated with coronary heart
of developing coronary heart disease is
the range of cholesterol levels and many
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s range.

to reduce both normal and elevated LDL-C
d from very low-density lipoprotein (VLDL)
ntly by the high affinity LDL receptor. The
ring effect of lovastatin may involve both
ration, and induction of the LDL receptor,
in and/or increased catabolism of LDL-C.
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ains one molecule of apolipoprotein B, and
s found in other lipoproteins, this strongly
s not merely cause cholesterol to be lost
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modestly reduces VLDL-C and plasma
I-III under **Clinical Studies**). The effects of
rogen, and certain other independent
coronary heart disease are unknown.

ibitor of HMG-CoA reductase, the enzyme
sion of HMG-CoA to mevalonate. The
o mevalonate is an early step in the
lesterol.

statin is a lactone which is readily
corresponding β-hydroxyacid, a potent
se. Inhibition of HMG-CoA reductase is the
nacokinetic studies of the β-hydroxyacid
and, following base hydrolysis, active plus
ers) in plasma following administration of

^{14}C-labeled lovastatin in man, 10% of the
and 83% in feces. The latter represents
creted in bile, as well as any unabsorbed
of total radioactivity (lovastatin plus ^{14}C-
ers and declined rapidly to about 10% of
bsorption of lovastatin, estimated relative
ose, in each of four animal species tested,
oral dose. In animal studies, after oral
selectivity for the liver, where it achieved
ntrations than in non-target tissues.
ive first-pass extraction in the liver, its
bsequent excretion of drug equivalents in
extensive hepatic extraction of lovastatin,
general circulation is low and variable. In a
hypercholesterolemic patients, it was
of an oral dose of lovastatin reaches the
inhibitors. Following administration of
nt of variation, based on between-subject
40% for the area under the curve (AUC) of
general circulation.

hydroxyacid metabolite are highly bound
proteins. Animal studies demonstrated that
rrain and placental barriers.

tes present in human plasma are the β-
6'-hydroxy derivative, and two additional
oncentrations of both active and total
2 to 4 hours of dose administration. While
dose range is 10 to 80 mg/day, linearity
general circulation was established by
ng lovastatin tablet dosages from 60 to
a once-a-day dosing regimen, plasma
itors over a dosing interval achieved a
ond and third days of therapy and were
ing a single dose. When lovastatin was
, plasma concentrations of total inhibitors
thirds those found when lovastatin was
r a standard test meal.

th severe renal insufficiency (creatinine
plasma concentrations of total inhibitors
were approximately two-fold higher than

erly patients between 70-78 years of age
g/day, the mean plasma level of HMG-CoA
y was increased approximately 45%
compared with 18 patients between 18-30 years of age (see **PRECAUTIONS, Geriatric Use**).

Lovastatin is a substrate for cytochrome P450 isoform 3A4 (CYP3A4) (see **PRECAUTIONS, Drug Interactions**). Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. In one study**, 10 subjects consumed 200 mL of double-strength grapefruit juice (one can of frozen concentrate diluted with one rather than 3 cans of water) three times daily for 2 days and an additional 200 mL double-strength grapefruit juice together with and 30 and 90 minutes following a single dose of 80 mg lovastatin on the third day. This regimen of grapefruit juice resulted in a mean increase in the serum concentration of lovastatin and its β-hydroxyacid metabolite (as measured by the area under the concentration-time curve) of 15-fold and 5-fold, respectively [as measured using a chemical assay - high performance liquid chromatography]. In a second study, 15 subjects consumed one 8 oz glass of single-strength grapefruit juice (one can of frozen concentrate diluted with 3 cans of water) with breakfast for 3 consecutive days and a single dose of 40 mg lovastatin in the evening of the third day. This regimen of grapefruit juice resulted in a mean increase in the plasma concentration (as measured by the area under the concentration-time curve) of active and total HMG-CoA reductase inhibitory activity [using an enzyme inhibition assay both before (for active inhibitors) and after (for total inhibitors) base hydrolysis] of 1.34-fold and 1.36-fold, respectively, and of lovastatin and its β-hydroxyacid metabolite [measured using a chemical assay – liquid chromatography/tandem mass spectrometry - different from that used in the first** study] of 1.94-fold and 1.57-fold, respectively. The effect of amounts of grapefruit juice between those used in these two studies on lovastatin pharmacokinetics has not been studied.

**Kantola, T, et al., Clin Pharmacol Ther 1998; 63(4): 397-402

Clinical Studies: Lovastatin has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of primary hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during continuation of therapy. Single daily doses given in the evening were more effective than the same dose given in the morning, perhaps because cholesterol is synthesized mainly at night.

In multicenter, double-blind studies in patients with familial or non-familial hypercholesterolemia, lovastatin, administered in doses ranging from 10 mg q.p.m. to 40 mg b.i.d., was compared to placebo. Lovastatin consistently and significantly decreased plasma total-C, LDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio. In addition, lovastatin produced increases of variable magnitude in HDL-C, and modestly decreased VLDL-C and plasma TG (see Tables I through III for dose response results).

The results of a study in patients with primary hypercholesterolemia are presented in Table I.

TABLE I

Lovastatin vs. Placebo

(Mean Percent Change from Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	TG.
Placebo	33	-2	-1	-1	0	+1	+9
Lovastatin							
10 mg q.p.m.	33	-16	-21	+5	-24	-19	-10
20 mg q.p.m.	33	-19	-27	+6	-30	-23	+9
10 mg b.i.d.	32	-19	-28	+8	-33	-25	-7
40 mg q.p.m.	33	-22	-31	+5	-33	-25	-8
20 mg b.i.d.	36	-24	-32	+2	-32	-24	-6

Lovastatin was compared to cholestyramine in a randomized open parallel study. The study was performed with patients with hypercholesterolemia who were at high risk of myocardial infarction. Summary results are presented in Table II.

TABLE II

Lovastatin vs. Cholestyramine

(Percent Change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TG. (mean)
Lovastatin								
20 mg b.i.d.	85	-27	-32	+9	-36	-31	-34	-21
40 mg b.i.d.	88	-34	-42	+8	-44	-37	-31	-27
Cholestyramine								
12 g b.i.d.	88	-17	-23	+8	-27	-21	+2	+11

Lovastatin was studied in controlled trials in hypercholesterolemic patients with well-controlled non-insulin dependent diabetes mellitus with normal renal function. The effect of lovastatin on lipids and lipoproteins and the safety profile of lovastatin were similar to that demonstrated in studies in nondiabetics. Lovastatin had no clinically important effect on glycemic control or on the dose requirement of oral hypoglycemic agents.

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Lovastatin was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2 mmol/L - 7.6 mmol/L], LDL-C >160 mg/dL [4.1 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. All changes in the lipid measurements (Table III) in lovastatin treated patients were dose-related and significantly different from placebo (p≤0.001). These results were sustained throughout the study.

TABLE III

Lovastatin vs. Placebo

(Percent Change from Baseline — Average Values Between Weeks 12 and 48)

DOSAGE	N**	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TG. (median)
Placebo	1663	+0.7	+0.4	+2.0	+0.2	+0.6	+4
Lovastatin							
20 mg q.p.m.	1642	-17	-24	+6.6	-27	-21	-10
40 mg q.p.m.	1645	-22	-30	+7.2	-34	-26	-14
20 mg b.i.d.	1646	-24	-34	+8.6	-38	-29	-16
40 mg b.i.d.	1649	-29	-40	+9.5	-44	-34	-19

**Patients enrolled

Atherosclerosis: In the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), the effect of therapy with lovastatin on coronary atherosclerosis was assessed by coronary angiography in hyperlipidemic patients. In the randomized, double-blind, controlled clinical trial, patients were treated with conventional measures (usually diet and 325 mg of aspirin every other day) and either lovastatin 20-80 mg daily or placebo. Angiograms were evaluated at baseline and at two years by computerized quantitative coronary angiography (QCA). Lovastatin significantly slowed the progression of lesions as measured by the mean change per-patient in minimum lumen diameter (the primary endpoint) and percent diameter stenosis, and decreased the proportions of patients categorized with disease progression (33% vs. 50%) and with new lesions (16% vs. 32%).

In a similarly designed trial, the Monitored Atherosclerosis Regression Study (MARS), patients were treated with diet and either lovastatin 80 mg daily or placebo. No statistically significant difference between lovastatin and placebo was seen for the primary endpoint (mean change per patient in percent diameter stenosis of all lesions), or for most secondary QCA endpoints. Visual assessment by angiographers who formed a consensus opinion of overall angiographic change (Global Change Score) was also a secondary endpoint. By this endpoint, significant slowing of disease was seen, with regression in 23% of patients treated with lovastatin compared to 11% of placebo patients.

In the Familial Atherosclerosis Treatment Study (FATS), either lovastatin or niacin in combination with a bile acid sequestrant for 2.5 years in hyperlipidemic subjects significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions by QCA compared to diet and, in some cases, low-dose resin.

The effect of lovastatin on the progression of atherosclerosis in the coronary arteries has been corroborated by similar findings in another vasculature. In the Asymptomatic Carotid Artery Progression Study (ACAPS), the effect of therapy with lovastatin on carotid atherosclerosis was assessed by B-mode ultrasonography in hyperlipidemic patients with early carotid lesions and without known coronary heart disease at baseline. In this double-blind, controlled clinical trial, 919 patients were randomized in a 2 x 2 factorial design to placebo, lovastatin 10-40 mg daily and/or warfarin. Ultrasonograms of the carotid walls were used to determine the change per patient from baseline to three years in mean maximum intimal-medial thickness (IMT) of 12 measured segments. There was a significant regression of carotid lesions in patients receiving lovastatin alone compared to those receiving placebo alone (p=0.001). The predictive value of changes in IMT for stroke has not yet been established. In the lovastatin group there was a significant reduction in the number of patients with major cardiovascular events relative to the placebo group (5 vs.14) and a significant reduction in all-cause mortality (1 vs. 8).

Eye: There was a high prevalence of baseline lenticular opacities in the patient population included in the early clinical trials with lovastatin. During these trials the appearance of new opacities was noted in both the lovastatin and placebo groups. There was no clinically significant change in visual acuity in the patients who had new opacities reported nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity.

A three-year, double-blind, placebo-controlled study in hypercholesterolemic patients to assess the effect of lovastatin on the human lens demonstrated that there were no clinically or statistically significant differences between the lovastatin and placebo groups in the incidence, type or progression of lenticular opacities. There are no controlled clinical data assessing the lens available for treatment beyond three years.

INDICATIONS AND USAGE:

Therapy with lovastatin should be a component of multiple risk factor intervention in those individuals with dyslipidemia at risk for atherosclerotic vascular disease. Lovastatin should be used in addition to a diet restricted in saturated fat and cholesterol as part of a treatment strategy to lower total-C and LDL-C to target levels when the response to diet and other nonpharmacological measures alone has been inadequate to reduce risk.

Coronary Heart Disease: Lovastatin is indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total-C and LDL-C to target levels.

Hypercholesterolemia: Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lovastatin tablets are indicated as an adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb***), when the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.

General Recommendations: Prior to initiating therapy with lovastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL(<4.5 mmol/L), LDL-C can be estimated using the following equation:

LDL-C = total-C - [0.2 x TG + HDL-C]

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, lovastatin tablets are not indicated.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

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

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD† or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional)††
2 + Risk factors (10 year risk ≤20%)	<130	≥130	10-year risk 10-20%: ≥130 10-year risk <10%: ≥160
0-1 Risk factor†††	<160	≥160	≥190 (160-189: LDL-Lowering drug optional)

† CHD, coronary heart disease

†† Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.

††† Almost all people with 0-1 risk factor have a 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

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

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

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy.

Although lovastatin may be useful to reduce elevated LDL-C levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL or IDL (i.e., hyperlipoproteinemia types I, III, IV, or V).***

***Classification of Hyperlipoproteinemias

Type	Lipoproteins elevated	Lipid Elevations major	Lipid Elevations minor
I	chylomicrons	TG	↑→ C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	↑→ C
V (rare)	chylomicrons, VLDL	TG	↑→ C

IDL=intermediate-density lipoprotein

CONTRAINDICATIONS:

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see **WARNINGS**).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as lovastatin to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, lovastatin is contraindicated during pregnancy and in nursing mothers. **Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, lovastatin should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see **PRECAUTIONS, Pregnancy**).

WARNINGS:

Skeletal Muscle: Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (> 10X the upper limit of normal [ULN]). **Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time.** In the EXCEL study, there was one case of myopathy among 4933 patients randomized to lovastatin 20-40 mg daily for 48 weeks, and 4 among 1649 patients randomized to 80 mg daily. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and creatine kinase (CK) increases promptly resolved. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the EXCEL study design.

Myopathy Caused by Drug Interactions: The incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid).

In addition, the risk of myopathy may be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Lovastatin is metabolized by the cytochrome P450 isoform 3A4 (CYP3A4). Potent inhibitors of this metabolic pathway can raise the plasma level of HMG-CoA reductase inhibitory activity and may increase the risk of myopathy. These include cyclosporine; the azole antifungals, itraconazole, and ketoconazole; the macrolide antibiotics, erythromycin and clarithromycin; HIV protease inhibitors; the antidepressant nefazodone; and large quantities of grapefruit juice (>1 quart daily) (see below; **CLINICAL PHARMACOLOGY, Pharmacokinetics; PRECAUTIONS, Drug Interactions; and DOSAGE AND ADMINISTRATION**).

Although the data are insufficient for lovastatin, the risk of myopathy appears to be increased when verapamil is used concomitantly with a closely related HMG-CoA reductase inhibitor (see **PRECAUTIONS, Drug Interactions**).

Reducing the Risk of Myopathy:

1. General measures. Patients starting therapy with lovastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness. A creatine kinase (CK) level above 10X ULN in a patient with unexplained muscle symptoms indicates myopathy. **Lovastatin therapy should be discontinued if myopathy is diagnosed or suspected.** In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved.

Of the patients with rhabdomyolysis, many had complicated medical histories. Some had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with lovastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. Measures to reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS, Drug Interactions). Physicians contemplating combined therapy with lovastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of lovastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of lovastatin have been used without myopathy in small, short-term clinical trials with careful monitoring. Addition of these drugs to lovastatin typically provides little additional reduction in LDL cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with lovastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of lovastatin should generally not exceed 20 mg/day (see **DOSAGE AND ADMINISTRATION** and **DOSAGE AND ADMINISTRATION, Concomitant Lipid-Lowering Therapy**), as the risk of myopathy increases substantially at higher doses. Concomitant use of lovastatin with itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) is not recommended. If no alternative to a short course of treatment with itraconazole, ketoconazole, erythromycin, or clarithromycin is available, a brief suspension of lovastatin therapy during such treatment can be considered as there are no known adverse consequences to brief interruptions of long-term cholesterol-lowering therapy.

Liver Dysfunction: Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in early clinical trials (see **ADVERSE REACTIONS**). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin, and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see **CLINICAL PHARMACOLOGY, Clinical Studies**), the incidence of persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with lovastatin, symptomatic liver disease has been reported rarely at all dosages (see **ADVERSE REACTIONS**).

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter (e.g., semiannually). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) returns to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of therapy with lovastatin is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with lovastatin (see **ADVERSE REACTIONS**). These changes appeared soon after initiation of therapy with lovastatin, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

PRECAUTIONS:

General: Lovastatin may elevate creatine phosphokinase and transaminase levels (see **WARNINGS** and **ADVERSE REACTIONS**). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia: Lovastatin is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. Lovastatin appears to be more likely to raise serum transaminases (see **ADVERSE REACTIONS**) in these homozygous patients.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness (see **WARNINGS, Skeletal Muscle**).

Drug Interactions:

Gemfibrozil and other fibrates, lipid-lowering doses (≥ 1g/day) of niacin (nicotinic acid): These drugs increase the risk of myopathy when given concomitantly with lovastatin, probably because they can produce myopathy when given alone (see **WARNINGS, Skeletal Muscle**). There is no evidence to suggest that these agents affect the pharmacokinetics of lovastatin.

CYP3A4 Interactions: Lovastatin has no CYP3A4 inhibitory activity; therefore, it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. However, lovastatin itself is a substrate for CYP3A4. Potent inhibitors of CYP3A4 may increase the risk of myopathy by increasing the plasma concentration of HMG-CoA reductase inhibitory activity during lovastatin therapy. These inhibitors include cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice (>1 quart daily) (see **CLINICAL PHARMACOLOGY, Pharmacokinetics** and **WARNINGS, Skeletal Muscle**).

Grapefruit juice contains one or more components that inhibit CYP3A4 and can increase the plasma concentrations of drugs metabolized by CYP3A4. Large quantities of grapefruit juice (>1 quart daily) significantly increase the serum concentrations of lovastatin and its β-hydroxyacid metabolite during lovastatin therapy and should be avoided; (see **CLINICAL PHARMACOLOGY, Pharmacokinetics** and **WARNINGS, Skeletal Muscle**).

Although the data are insufficient for lovastatin, the risk of myopathy appears to be increased when verapamil is used concomitantly with a closely related HMG-CoA reductase inhibitor (see **WARNINGS, Skeletal Muscle**).

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two-seconds increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Oral Hypoglycemic Agents: In pharmacokinetic studies of lovastatin in hypercholesterolemic non-insulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell 4chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose which produced plasma drug levels (C_{max}) which were about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Cataracts were seen in dogs treated for 11 and 28 weeks at 180 mg/kg/day and 1 year at 60 mg/kg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of lovastatin.)

There was an increase in incidence of papilloma in the non-glandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males at drug exposures between 2-7 times that of human exposure at 80 mg/day (doses in rats were 5, 30 and 180 mg/kg/day).

An increased incidence of thyroid neoplasms in rats appears to be a response that has been seen with other HMG-CoA reductase inhibitors.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high dose females and mid- and high dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See **CONTRAINDICATIONS**.

Safety in pregnant women has not been established.

Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review† of approximately 100 prospectively followed pregnancies in women exposed to lovastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with lovastatin during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soo pregnancy is recognized. Lovastatin should be administered to wo of child-bearing potential only when such patients are highly unlike conceive and have been informed of the potential hazards.

† Manson, J.M., Freyssinges. C., Ducrocq, M.B., Stephenson, W.P., Postmark Surveillance of Lovastatin and Simvastatin Exposure During Pregn Reproductive Toxicology. 10(6):439-446. 1996.

Nursing Mothers: It is not known whether lovastatin is excrete human milk. Because a small amount of another drug in this clas excreted in human breast milk and because of the potential for ser adverse reactions in nursing infants, women taking lovastatin should nurse their infants (see **CONTRAINDICATIONS**).

Pediatric Use: Safety and effectiveness in pediatric patients have been established. Because pediatric patients are not likely to benefit f cholesterol lowering for at least a decade and because experience this drug is limited (no studies on subjects below the age of 20 ye treatment of pediatric patients with lovastatin is not recommende this time.

Geriatric Use: A pharmacokinetic study with lovastatin showed mean plasma level of HMG-CoA reductase inhibitory activity to approximately 45% higher in elderly patients between 70-78 year age compared with patients between 18-30 years of age; howe clinical study experience in the elderly indicates that dosage adjustn based on this age-related pharmacokinetic difference is not needed clinical studies conducted with lovastatin, 21% of patients w ≥65 years of age. Lipid-lowering efficacy with lovastatin was at leas great in elderly patients compared with younger patients, and there v no overall differences in safety over the 20 to 80 mg/day dosage ra (see **CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS:

Lovastatin is generally well tolerated; adverse reactions usually h been mild and transient.

Phase III Clinical Studies: In Phase III controlled clinical stu involving 613 patients treated with lovastatin, the adverse experie profile was similar to that shown below for the 8,245-patient EX study (see **Expanded Clinical Evaluation of Lovastatin [EXCEL] Stu**

Persistent increases of serum transaminases have been noted (**WARNINGS, Liver Dysfunction**).

About 11% of patients had elevations of CK levels of at least tw the normal value on one or more occasions. The correspond values for the control agent cholestyramine was 9 percent. T was attributable to the noncardiac fraction of CK. Large increases in have sometimes been reported (see **WARNINGS, Skeletal Muscle**).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Stu

Lovastatin was compared to placebo in 8,245 patients w hypercholesterolemia (total-C 240-300 mg/dL [6.2-7.8 mmol/L]) in randomized, double-blind, parallel, 48-week EXCEL study. Clini adverse experiences reported as possibly, probably or definit drug-related in ≥1% in any treatment group are shown in the ta below. For no event was the incidence on drug and placebo statistic different.

	Placebo (N = 1663) %	Lovastatin 20 mg q.p.m. (N = 1642) %	Lovastatin 40 mg q.p.m. (N = 1645) %	Lovastatin 20 mg b.i.d. (N = 1646) %	Lovasta 40 m b.i.d. (N = 16 %
Body As a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably definitely drug-related in 0.5 to 1.0 percent of patients in any dru treated group as listed below. In all these cases the incidence on dr and placebo was not statistically different. *Body as a Whole:* chest pai *Gastrointestinal:* acid regurgitation, dry mouth, vomitin *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervou System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritu *Special Senses:* eye irritation.

In the EXCEL study (see **CLINICAL PHARMACOLOGY, Clinic Studies**), 4.6% of the patients treated up to 48 weeks were discontinue due to clinical or laboratory adverse experiences which were rated by t investigator as possibly, probably or definitely related to therapy wi lovastatin. The value for the placebo group was 2.5%.

Concomitant Therapy: In controlled clinical studies in whi lovastatin was administered concomitantly with cholestyramine, adverse reactions peculiar to this concomitant treatment were observe The adverse reactions that occurred were limited to those report previously with lovastatin or cholestyramine. Other lipid-lowering agen were not administered concomitantly with lovastatin during controll clinical studies. Preliminary data suggests that the addition gemfibrozil to therapy with lovastatin is not associated with great reduction in LDL-C than that achieved with lovastatin alone. uncontrolled clinical studies, most of the patients who have develope myopathy were receiving concomitant therapy with cyclosporin gemfibrozil or niacin (nicotinic acid) (see **WARNINGS, Skelet Muscle**).

The following effects have been reported with drugs in this class. N all the effects listed below have necessarily been associated wi lovastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysi arthralgias.

Neurological: dysfunction of certain cranial nerves (including alterati of taste, impairment of extra-ocular movement, facial paresis), trem dizziness, vertigo, memory loss, paresthesia, peripheral neuropath peripheral nerve palsy, psychic disturbances, anxiety, insomni depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome h

and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity: Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell 4chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose which produced plasma drug levels (C_{max}) which were about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

Cataracts were seen in dogs treated for 11 and 28 weeks at 180 mg/kg/day and 1 year at 60 mg/kg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of lovastatin.)

There was an increase in incidence of papilloma in the non-glandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males at drug exposures between 2-7 times that of human exposure at 80 mg/day (doses in rats were 5, 30 and 180 mg/kg/day).

An increased incidence of thyroid neoplasms in rats appears to be a response that has been seen with other HMG-CoA reductase inhibitors.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high dose females and mid- and high dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See **CONTRAINDICATIONS**.

Safety in pregnant women has not been established.

Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[1] of approximately 100 prospectively followed pregnancies in women exposed to lovastatin or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with lovastatin during pregnancy (see **CONTRAINDICATIONS**), treatment should be immediately discontinued as soon as pregnancy is recognized. Lovastatin should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

[1] Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy. Reproductive Toxicology. 10(6):439-446. 1996.

Nursing Mothers: It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking lovastatin should not nurse their infants (see **CONTRAINDICATIONS**).

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies on subjects below the age of 20 years), treatment of pediatric patients with lovastatin is not recommended at this time.

Geriatric Use: A pharmacokinetic study with lovastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age; however, clinical study experience in the elderly indicates that dosage adjustment based on this age-related pharmacokinetic difference is not needed. In clinical studies conducted with lovastatin, 21% of patients were ≥65 years of age. Lipid-lowering efficacy with lovastatin was at least as great in elderly patients compared with younger patients, and there were no overall differences in safety over the 20 to 80 mg/day dosage range (see **CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS:

Lovastatin is generally well tolerated; adverse reactions usually have been mild and transient.

Phase III Clinical Studies: In Phase III controlled clinical studies involving 613 patients treated with lovastatin, the adverse experience profile was similar to that shown below for the 8,245-patient EXCEL study (see **Expanded Clinical Evaluation of Lovastatin [EXCEL] Study**).

Persistent increases of serum transaminases have been noted (see **WARNINGS, Liver Dysfunction**).

About 11% of patients had elevations of CK levels of at least twice the normal value on one or more occasions. The corresponding values for the control agent cholestyramine was 9 percent. This was attributable to the noncardiac fraction of CK. Large increases in CK have sometimes been reported (see **WARNINGS, Skeletal Muscle**).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Lovastatin was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2-7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably or definitely drug-related in ≥1% in any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

	Placebo (N = 1663) %	Lovastatin 20 mg q.p.m. (N = 1642) %	Lovastatin 40 mg q.p.m. (N = 1645) %	Lovastatin 20 mg b.i.d. (N = 1646) %	Lovastatin 40 mg b.i.d. (N = 1649) %
Body As a Whole					
Asthenia	1.4	1.7	1.4	1.5	1.2
Gastrointestinal					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
Musculoskeletal					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
Nervous System/ Psychiatric					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
Skin					
Rash	0.7	0.8	1.0	1.2	1.3
Special Senses					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably or definitely drug-related in 0.5 to 1.0 percent of patients in any drug-treated group as listed below. In all these cases the incidence on drug and placebo was not statistically different. *Body as a Whole:* chest pain; *Gastrointestinal:* acid regurgitation, dry mouth, vomiting; *Musculoskeletal:* leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric:* insomnia, paresthesia; *Skin:* alopecia, pruritus; *Special Senses:* eye irritation.

In the EXCEL study (see **CLINICAL PHARMACOLOGY, Clinical Studies**), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences which were rated by the investigator as possibly, probably or definitely related to therapy with lovastatin. The value for the placebo group was 2.5%.

Concomitant Therapy: In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggests that the addition of gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL-C than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with cyclosporine, gemfibrozil or niacin (nicotinic acid) (see **WARNINGS, Skeletal Muscle**).

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with lovastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE:

After oral administration of lovastatin to mice, the median lethal dose observed was >15 g/m².

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5-6 g.

Until further experience is obtained, no specific treatment of overdosage with lovastatin can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION:

The patient should be placed on a standard cholesterol-lowering diet before receiving lovastatin and should continue on this diet during treatment with lovastatin (see NCEP Treatment Guidelines for details on dietary therapy). Lovastatin should be given with meals.

The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 10-80 mg/day in single or two divided doses; the maximum recommended dose is 80 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Guidelines and **CLINICAL PHARMACOLOGY**). Patients requiring reductions in LDL-C of 20% or more to achieve their goal (see **INDICATIONS AND USAGE**) should be started on 20 mg/day of lovastatin. A starting dose of 10 mg may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.

In patients taking cyclosporine concomitantly with lovastatin (see **WARNINGS, Skeletal Muscle**), therapy should begin with 10 mg of lovastatin and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of lovastatin if cholesterol levels fall significantly below the targeted range.

Concomitant Lipid-Lowering Therapy: Lovastatin is effective alone or when used concomitantly with bile-acid sequestrants. Use of lovastatin with fibrates or niacin should generally be avoided. However, if lovastatin is used in combination with fibrates or niacin, the dose of lovastatin should generally not exceed 20 mg/day (see **WARNINGS, Skeletal Muscle** and **PRECAUTIONS, Drug Interactions**).

Dosage in Patients with Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance <30 mL/min), dosage increases above 20 mg/day should be carefully considered and, if deemed necessary, implemented cautiously (see **CLINICAL PHARMACOLOGY** and **WARNINGS, Skeletal Muscle**).

HOW SUPPLIED:

Lovastatin Tablets, USP are available as follows:

10 mg — Each white, round, flat faced beveled edge tablet imprinted with *R* on one side and 633 on the other contains 10 mg of lovastatin. Tablets are supplied in bottles of 30 (NDC 0228-2633-03), 60 (NDC 0228-2633-06), and 100 (NDC 0228-2633-11) with a child-resistant closure and 100 (NDC 0228-2633-10), 500 (NDC 0228-2633-50), and 1000 (NDC 0228-2633-96) without a child-resistant closure.

20 mg — Each pink, round, flat faced beveled edge tablet imprinted with *R* on one side and 634 on the other contains 20 mg of lovastatin. Tablets are supplied in bottles of 30 (NDC 0228-2634-03), 60 (NDC 0228-2634-06), 90 (NDC 0228-2634-09), and 100 (NDC 0228-2634-11) with a child-resistant closure and 100 (NDC 0228-2634-10), 500 (NDC 0228-2634-50), and 1000 (NDC 0228-2634-96) without a child-resistant closure.

40 mg — Each yellow, round, flat faced beveled edge tablet imprinted with *R* on one side and 635 on the other contains 40 mg of lovastatin. Tablets are supplied in bottles of 30 (NDC 0228-2635-03), 60 (NDC 0228-2635-06), 90 (NDC 0228-2635-09) and 100 (NDC 0228-2635-11) with a child-resistant closure and 100 (NDC 0228-2635-10), 500 (NDC 0228-2635-50), and 1000 (NDC 0228-2635-96) without a child-resistant closure.

Dispense in a tight, light-resistant container as defined in the USP.

Store between 5°-30°C (41°-86°F). Protect from light and store in a well-closed, light-resistant container.

Rx only

Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
40-8856

Revised — November 2001

75-828

AP 12/17/01

PUREPAC

1000 Tablets NDC 0228-2635-96

LOVASTATIN
Tablets, USP

℞ only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 40 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
PHARMACIST: Container closure is not child-resistant.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Rev. 9/99
Lot No.:

DEC 17 2001
APPROVED
SAMPLE

3 0228-2635-96 4

PUREPAC

500 Tablets NDC 0228-2635-50

LOVASTATIN
Tablets, USP

℞ only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 40 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
PHARMACIST: Container closure is not child-resistant.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Rev. 9/99
Lot No.:

DEC 17 2001
APPROVED
SAMPLE

3 0228-2635-50 6

PUREPAC

100 Tablets NDC 0228-2635-10

LOVASTATIN
Tablets, USP

℞ only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 40 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
PHARMACIST: Container closure is not child-resistant.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Rev. 9/99
Lot No.:

DEC
APPROVED
SAMPLE

3 0228-2635-10 0

PUREPAC

90 Tablets NDC 0228-2635-09

LOVASTATIN
Tablets, USP

℞ only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 40 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Rev. 9/99
Lot No.:

DEC
APPROVED
SAMPLE

3 0228-2635-09 4

PUREPAC

60 Tablets NDC 0228-2635-06

LOVASTATIN
Tablets, USP

℞ only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 40 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Rev. 9/99
Lot No.:

DEC 17 2001
APPROVED
SAMPLE

3 0228-2635-06 3

PUREPAC

30 Tablets NDC 0228-2635-03

LOVASTATIN
Tablets, USP

℞ only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 40 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Rev. 9/99
Lot No.:

DEC
SAMPLE

3 0228-2635-03 2

75-828
AP 12/17/01

PUREPAC

1000 Tablets NDC 0228-2634-96

LOVASTATIN
Tablets, USP

20 mg

Rx only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 20 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
PHARMACIST: Container closure is not child-resistant.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Lot No.:
Rev. 9/99

SAMPLE

3 0228-2634-96 7

DEC 7 2001
APPROVED

PUREPAC

500 Tablets NDC 0228-2634-50

LOVASTATIN
Tablets, USP

20 mg

Rx only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 20 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
PHARMACIST: Container closure is not child-resistant.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Lot No.:
Rev. 9/99

SAMPLE

3 0228-2634-50 9

PUREPAC

100 Tablets NDC 0228-2634-10

LOVASTATIN
Tablets, USP

20 mg

Rx only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 20 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
PHARMACIST: Container closure is not child-resistant.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Lot No.:
Rev. 9/99

SAMPLE

3 0228-2634-10 3

PUREPAC

90 Tablets NDC 0228-2634-09

LOVASTATIN
Tablets, USP

20 mg

Rx only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 20 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Lot No.:
Rev. 9/99

SAMPLE

3 0228-2634-09 7

DEC 7 2001
APPROVED

PUREPAC

60 Tablets NDC 0228-2634-06

LOVASTATIN
Tablets, USP

20 mg

Rx only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 20 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Lot No.:
Rev. 9/99

SAMPLE

3 0228-2634-06 6

DEC 7 2001
APPROVED

PUREPAC

30 Tablets NDC 0228-2634-03

LOVASTATIN
Tablets, USP

20 mg

Rx only

EACH TABLET CONTAINS:
Lovastatin, USP ..... 20 mg
Dispense in a tight, light-resistant container as defined in the USP.
USUAL DOSAGE: See accompanying circular.
Store between 5°-30°C (41°-86°F).
Protect from light and store in a well-closed, light-resistant container.
Manufactured by:
PUREPAC PHARMACEUTICAL CO.
Elizabeth, NJ 07207 USA
Lot No.:
Rev. 9/99

SAMPLE

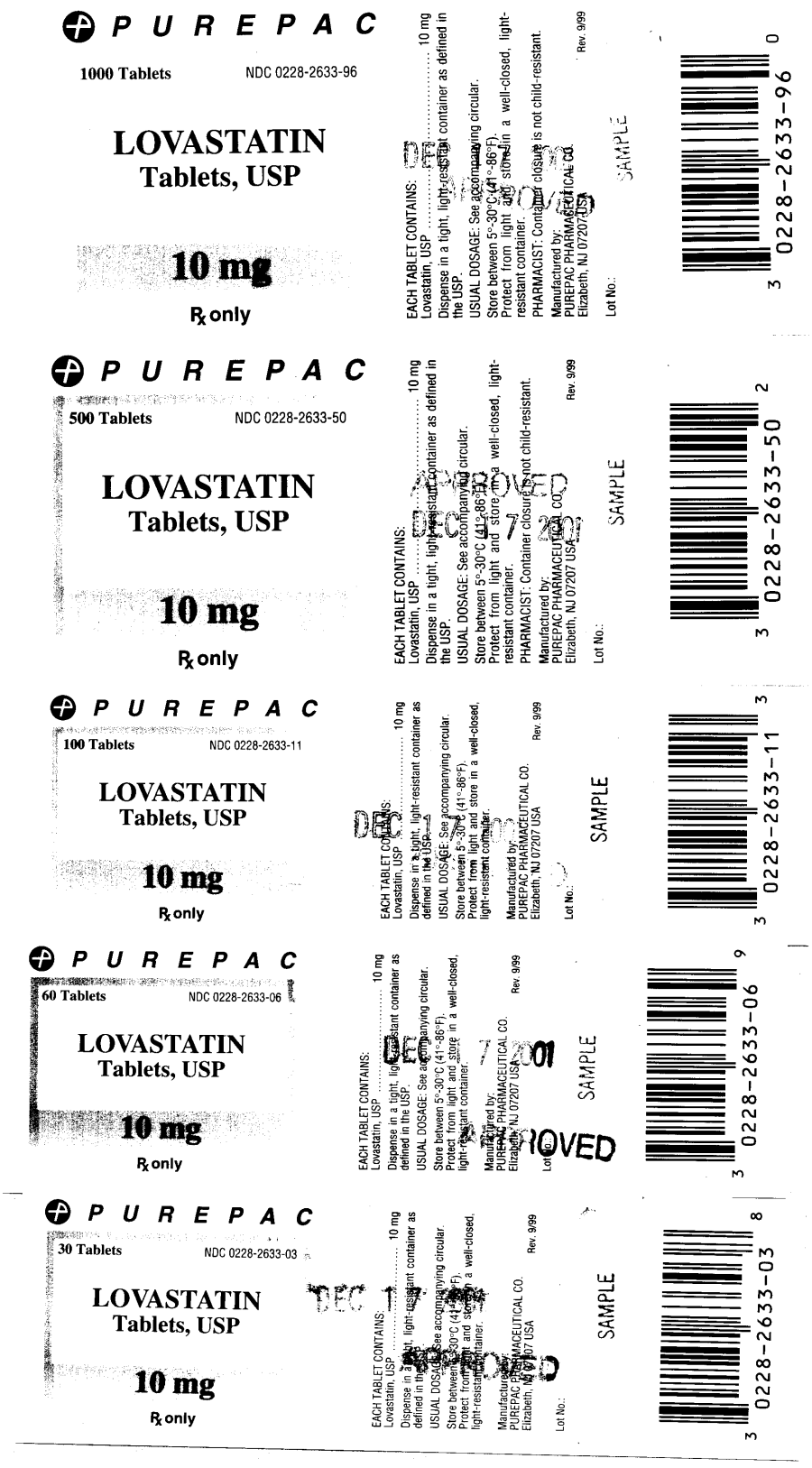
3 0228-2634-03 5

APPROVED
DEC 17 2001

75-828

AP

12/17/01



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-828

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1 2. ANDA # **75828**

3. NAME AND ADDRESS OF APPLICANT
Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 7207

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Mevacor Tablets; 10, 20 & 40 mg
Innovator Company: Merck Research Laboratories, Div. Merck and Co. Inc.
Patent and Expiration Date: #4231938: 06/15/01
Additional Marketing Exclusivity: An indication for "primary prevention of coronary heart disease in patients without symptomatic cardiovascular disease who have average to moderately elevated Total-C and LDL-C and below average HDL-C" expires on 3/11/02.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR:

9. AMENDMENTS AND OTHER DATES:

FIRM:

3/29/00	Original ANDA Submission
4/12/00	Field Copy Submission and Cert. Of Financial Int.
4/17/00	New Correspondence (ESD)
6/28/00	Bioequivalence Amendment

FDA:

3/30/00	EER Submitted
4/19/00	Receipt of ANDA Acknowledgement
6/5/00	Bioequivalence Deficiencies
8/21/00	Bioequivalence is Adequate.
7/10/00	Labeling Review/Deficiencies

10. PHARMACOLOGICAL CATEGORY
Cholesterol lowering agent.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF number	DMF type	DMF holder	Subject	LOA's

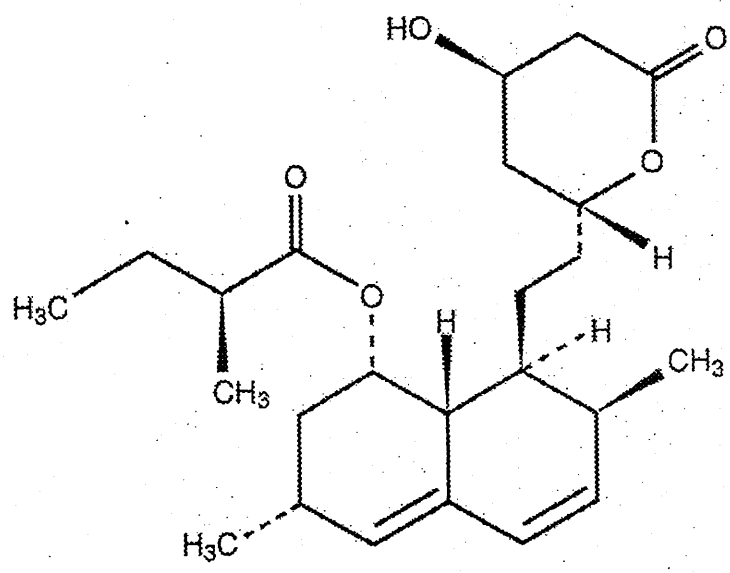
13. DOSAGE FORM: Oral Tablet

14. STRENGTH: 10 mg, 20 mg, and 40 mg

15. CHEMICAL NAME AND STRUCTURE

Chemical name: 1S-[1α(R*), 3α,7β,8β (2S*,4S*), 8aβ]]-1,2,3,7,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate.

Chemical structure:



Formula: $C_{24}H_{36}O_5$

Molecular weight: 404.55

CAS registry number(s): 75330-75-5

16. RECORDS AND REPORTS: N/A

17. COMMENTS
See Item #38

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable; FAX Amendment

19. REVIEWER: Kenneth J. Furnkranz
DATE COMPLETED: 9/12/00
DATE REVISED: 9/15/00

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1. CHEMISTRY REVIEW NO. 2 2. ANDA # 75828

3. NAME AND ADDRESS OF APPLICANT
Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 7207

4. LEGAL BASIS FOR SUBMISSION
Innovator Product: Mevacor Tablets; 10, 20 & 40 mg
Innovator Company: Merck Research Laboratories,
Patent and Expiration Date: #4231938: 06/15/01
Additional Marketing Exclusivity: An indication for "primary prevention of coronary heart disease in patients without symptomatic cardiovascular disease who have average to moderately elevated Total-C and LDL-C and below average HDL-C" expires on 3/11/02.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME Lovastatin Tabs USP; 10, 20 & 40 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

3/29/00	Original ANDA Submission
4/12/00	Field Copy and Cert. Of Financial Interests.
4/17/00	New Correspondence (ESD)
6/28/00	Bioequivalence Amendment
*10/19/00	Original ANDA Amend. Response to N/A #1 FAX

FDA:

4/19/00	EER Submitted to OC
4/19/00	Receipt of ANDA Acknowledgement
6/5/00	Bioequivalence Deficiencies
7/10/00	Labeling Review/Deficiencies
8/21/00	Bio is Adequate (no further questions)
9/21/00	Chemistry Review #1 (FAX Deficiencies)

10. PHARMACOLOGICAL CATEGORY
Cholesterol lowering agent.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

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ON ORIGINAL

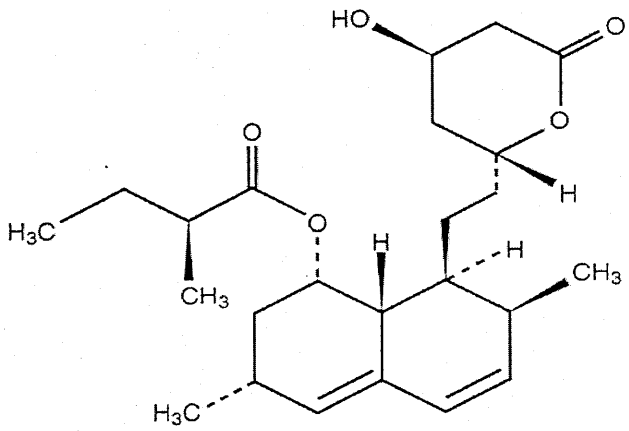
DMF #	Type	DMF holder	Subject	LOA's
[redacted]				

13. DOSAGE FORM: Oral Tablet 14. STRENGTH: 10, 20 & 40mg

15. CHEMICAL NAME AND STRUCTURE

Chemical name: 1S-[1α(R*), 3α,7β,8β (2S*,4S*), 8aβ]]-1,2,3,7,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate.

Chemical structure:



APPEARS THIS WAY ON ORIGINAL

Formula: $C_{24}H_{36}O_5$
Molecular weight: 404.55
CAS registry number(s): 75330-75-5

16. RECORDS AND REPORTS: N/A

17. COMMENTS: See Item #38

18. CONCLUSIONS AND RECOMMENDATIONS: Chemistry Closed. Pending Labeling and EER

19. REVIEWER: Kenneth J. Furnkranz
DATE COMPLETED: 10/25/00

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Chemistry Closed

1. CHEMISTRY REVIEW NO. 3 2. ANDA # 75828

3. NAME AND ADDRESS OF APPLICANT
Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 7207

4. LEGAL BASIS OF SUBMISSION:
Innovator Product: Mevacor Tablets; 10, 20 & 40 mg
Innovator Company: Merck Research Laboratories,
Patent and Expiration Date: #4231938: 06/15/01
Additional Marketing Exclusivity: N/A.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME Lovastatin Tabs USP; 10, 20 & 40 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
3/29/00 Original ANDA Submission
*6/14/01 ANDA MINOR Amendment (Update TA to Final AP).

10. PHARMACOLOGICAL CATEGORY
Cholesterol lowering agent.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s): See the Chemistry Review #2

13. DOSAGE FORM: Oral Tablet 14. STRENGTH: 10, 20 & 40mg

15. CHEMICAL NAME AND STRUCTURE
Chemical name: 1S-[1α(R*), 3α,7β,8β (2S*,4S*), 8aβ]]-1,2,3,7,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate.
Formula: $C_{24}H_{36}O_5$
Molecular weight: 404.55
CAS registry number(s): 75330-75-5

16. RECORDS AND REPORTS: N/A

17. COMMENTS: See Item #38

18. CONCLUSIONS AND RECOMMENDATIONS: Chemistry Closed; Labeling Pending.

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1. CHEMISTRY REVIEW NO. 4 2. ANDA # **75828**

3. NAME AND ADDRESS OF APPLICANT
Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 7207

4. LEGAL BASIS OF SUBMISSION:
Innovator Product: Mevacor Tablets; 10, 20 & 40 mg
Innovator Company: Merck Research Laboratories,

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME Lovastatin Tablets USP; 10, 20 & 40 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:

3/29/00	Original ANDA Submission
6/14/01	ANDA MINOR Amendment (Update TA to Final AP).
*8/20/01	ANDA Minor Amendment; Satisfactory Inspection Affirmation

10. PHARMACOLOGICAL CATEGORY
Cholesterol lowering agent.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s): See the Chemistry Review #2

13. DOSAGE FORM: Oral Tablet 14. STRENGTH: 10, 20 & 40mg

15. CHEMICAL NAME AND STRUCTURE: See previous review.

16. RECORDS AND REPORTS: N/A

17. COMMENTS: See Item #38

18. CONCLUSIONS AND RECOMMENDATIONS: 2nd Tentative Approval.

19. REVIEWER: K. J. Furnkranz DATE COMPLETED: 9/5/01

20. COMPONENTS AND COMPOSITION: No change from C.R.#3).

21. FACILITIES AND PERSONNEL: N/C from Chemistry Rev. #3.

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1. CHEMISTRY REVIEW NO. 5 2. ANDA # **75828**

3. NAME AND ADDRESS OF APPLICANT
Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 7207

4. LEGAL BASIS OF SUBMISSION:
Innovator Product: Mevacor Tablets; 10, 20 & 40 mg
Innovator Company: Merck Research Laboratories,

U.S. Patent #4231938 expired on June 15, 2001.
Pediatric Exclusivity expires on 12/15/01.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME Lovastatin Tablets USP; 10, 20 & 40 mg

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
FIRM:
3/29/00 Original ANDA Submission
6/14/01 ANDA MINOR Amendment (Update TA to Final AP).
8/20/01 ANDA Minor Amendment; Satisfactory Inspection Affirmation
*10/26/01 ANDA MINOR Amendment (CMC Information)

10. PHARMACOLOGICAL CATEGORY
Cholesterol lowering agent.

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s): See the Chemistry Review #2

13. DOSAGE FORM: Oral Tablet 14. STRENGTH: 10, 20 & 40mg

15. CHEMICAL NAME AND STRUCTURE: See previous review.

16. RECORDS AND REPORTS: N/A

17. COMMENTS: See Item #38

18. CONCLUSIONS AND RECOMMENDATIONS: Approval (pending expiration of Pediatric Exclusivity on 12/15/01).

19. REVIEWER: K. J. Furnkranz DATE COMPLETED: 11/7/01

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-828

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-828 SPONSOR : Purepac

DRUG AND DOSAGE FORM : Lovastatin Tablets

STRENGTH(S) : 10 mg, 20 mg, 40 mg

TYPES OF STUDIES : Fasting and non-fasting

CLINICAL STUDY SITE(S) : —

ANALYTICAL SITE(S) : —

STUDY SUMMARY : The fasting and non-fasting studies are acceptable.

DISSOLUTION : The test products meet USP specifications: NLT — (Q) in 30 minutes. The waivers of *in vivo* bioequivalence study requirements for 10 and 20 mg tablets are granted.

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic No New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : K. Dhariwal BRANCH : II

INITIAL : ____ /S/ _____ DATE : 7/28/00

TEAM LEADER : S. Nerurkar BRANCH : II

INITIAL : /S/ DATE : 7/31/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : _ /S/ _____ DATE : 8/2/00

9.1

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-828 APPLICANT: Purepac

DRUG PRODUCT: Lovastatin Tablets, USP
10 mg, 20 mg, 40 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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ON ORIGINAL

CC: ANDA 75828
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

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Printed in final on 07/28/00

/S/ 7/31/00

Endorsements: (Final with Dates)
HFD-655/ Dhariwal /S/ 7/28/00
HFD-655/ Nerurkar
HFD-650/ D. Conner /S/ 8/21/00

BIOEQUIVALENCY - ACCEPTABLE

Submission date: June 28, 2000

1. **STUDY AMENDMENT** (STA)

✓ Strengths: 10 mg, 20 mg, 40 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

WinBio Comments:

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Lovastatin Tablets, USP
10 mg, 20 mg, 40 mg
ANDA #75-828
Reviewer: Kuldeep R. Dhariwal
File name: 75828SDW.600

Purepac Pharmaceuticals
2000 Elmora Avenue
Elizabeth, NJ 07207
Submission Date:
June 28, 2000

Review of an Amendment

Background:

March 29, 2000: Original submission.
40 mg tablets: Dissolution data and *in vivo* bioequivalence studies measuring lovastatin and metabolite, beta-hydroxylovastatin under fasting and non-fasting conditions.
10 mg and 20 mg tablets: Dissolution data and waiver requests for *in vivo* bioequivalence study requirements.
June 5, 2000: The following bioequivalence deficiencies were communicated to the firm:

1. Fasting and non-fasting studies: You are requested to calculate elimination rate constant, AUC_{0-inf}, and elimination half-life of lovastatin as well as beta-hydroxylovastatin. Please include these data with other pharmacokinetic parameters and submit the revised data files.
2. Fasting and non-fasting studies: Please submit linear plots of individual subject plasma profiles for lovastatin and beta-hydroxylovastatin.

June 28, 2000: This amendment containing the information requested by the Division of Bioequivalence (DBE).

Review of amendment:

Bioequivalence study under fasting conditions:

Lovastatin:

Pharmacokinetic Parameters:	Table 1
90% Confidence Intervals:	Table 1

Beta-Hydroxylovastatin:

Pharmacokinetic Parameters:	Table 2
90% Confidence Intervals:	Table 2

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3. The dissolution testing conducted by Purepac on its lovastatin 10 mg, 20 mg, and 40 mg tablets is acceptable. The firm has conducted an acceptable *in vivo* bioequivalence study comparing its 40 mg tablets with 40 mg tablets of the reference product Mevacor® manufactured by Merck. The formulations for the 10 and 20 mg tablets are proportionally similar to the 40 mg tablet, which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 10, 20, and 40 mg test tablets is granted. The 10 and 20 mg tablets of the test product are therefore deemed bioequivalent to the 10 and 20 mg tablets of Mevacor® manufactured by Merck.
4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The

[ ]

Not less than ~ (Q) of the labeled amount of lovastatin in the dosage form is dissolved in 30 minutes.

5. From bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

/S/ 7/28/00

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

/S/ Date 7/31/2000

Concur: /S/ Date 8/21/00

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Table 1. FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992259
LEAST-SQUARES MEANS FOR PHARMACOKINETIC PARAMETERS
LOVASTATIN
(N = 47[1])

	ln AUC 0-t[2] (ng·h/mL)	ln Cmax[2] (ng/mL)	tmax (h)	ln AUCinf[2] (ng·h/mL)	kel (1/h)	half-life (h)
Purepac (A)						
Mean	39.438	2.6765	4.894	44.054	0.09407	9.240
CV%	66.1	59.6	68.2	60.9	48.1	51.9
n[1]	94	94	94	80	80	80
Merck&Co (B)						
Mean	34.529	2.6120	5.660	41.135	0.08208	10.272
CV%	68.9	70.8	104.1	62.5	46.3	48.2
n[1]	94	94	94	74	74	74
Least-Squares Means						
Purepac (A)	39.4545	2.67776		42.5691		
Merck&Co (B)	34.5864	2.61501		39.6193		
Ratio of Least-Squares Means (A/B)%	114.1	102.4		107.4		
90% Confidence Intervals (A/B)%						
Lower limit:	107.3	94.9		99.5		
Upper limit:	121.3	110.5		116.0		
p-value (ANOVA)						
A vs B	0.0007	0.6036		0.1226		
Period	0.0135	0.0188		0.5731		
Sequence	0.5536	0.6272		0.7978		
Intrasubject CV%	33.1	32.7		28.1		

1. N is the number of subjects and n is the number of observations
2. For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Arithmetic Means			
Parameter	A	B	Ratio
AUC_{0-t}	47.330	41.914	1.129
AUC_{0-inf}	50.273	46.663	1.118
C_{max}	3.103	3.231	0.960
T_{max}	4.894	5.66	

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ON ORIGINAL

Table 2. FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992259
LEAST-SQUARES MEANS FOR PHARMACOKINETIC PARAMETERS
Beta-HYDROXYLOVASTATIN
(N = 47[1])

	ln AUC 0-t[2] (ng·h/mL)	ln Cmax[2] (ng/mL)	Tmax (h)	ln AUCinf[2] (ng·h/mL)	kel (1/h)	half-life (h)
Purepac (A)						
Mean	33.094	2.4653	5.324	38.700	0.08906	10.570
CV%	60.6	50.4	83.0	56.6	62.6	58.6
n[1]	94	94	94	65	65	65
Merck&Co (B)	31.608	2.6509	5.288	38.273	0.07322	15.404
Mean	67.4	56.3	90.5	56.2	55.6	115.0
CV%	94	94	94	68	68	68
n[1]						
Least-Squares Means						
Purepac (A)	33.1932	2.4700		37.5087		
Merck&Co (B)	31.6722	2.6524		37.2057		
Ratio of Least-Squares Means (A/B)%	104.8	93.1		100.8		
90% Confidence Intervals (A/B)%						
Lower limit:	98.9	86.7		93.6		
Upper limit:	111.1	100.0		108.6		
p-value (ANOVA)						
A vs B	0.1842	0.1018		0.8542		
Period	0.4176	0.9655		0.0971		
Sequence	0.1415	0.3697		0.2786		
Intrasubject CV%	26.3	28.1		24.2		

1. N is the number of subjects and n is the number of observations
2. For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Arithmetic Means			
Parameter	A	B	Ratio
AUC_{0-t}	38.810	38.131	1.02
AUC_{0-inf}	42.325	44.813	1.03
C_{max}	2.784	3.057	0.91
T_{max}	5.324	5.288	

Table 3. FED/FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992517
ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS
FOR LOVASTATIN IN 23 SUBJECTS

PK PARAMETER	N	TEST TREATMENT A	N	TEST TREATMENT B	N	REFERENCE TREATMENT C	RATIO (B/A)%	RATIO (B/C)%
AUCT [ng•hr/mL]	23	66.94 (67.9)	23	44.73 (89.9)	23	48.01 (80.8)	66.8	93.2
Cmax [ng/mL]	23	3.7600 (44.8)	23	8.8168 (66.2)	23	10.1587 (55.8)	234.5	86.8
Tmax [hr]	23	8.891 (73.2)	23	2.478 (45.3)	23	1.783 (45.4)	27.9	139.0
AUCinf [ng•hr/mL]	19	71.11 (65.3)	19	53.18 (83.3)	17	51.61 (82.0)	74.8	103.0
kel [1/h]	19	0.09223 (44.3)	19	0.13231 (128.2)	17	0.11471 (82.0)	143.5	115.3
Half-life (h)	19	9.007 (43.1)	19	14.502 (175.3)	17	8.744 (49.7)	161.0	165.9

LEAST-SQUARES MEANS FOR PHARMACOKINETIC PARAMETERS
LOVASTATIN (N=23)*

	ln AUC_{0-t}* ng·h/mL (%CV)	ln AUC_{0-inf}* ng.h/mL (%CV)	ln C_{max}* ng/mL (%CV)	T_{max} h (%CV)
Mean				
Purepac:fast (A)	55.420 (70)	60.713(61)	3.46437 (42.5)	8.891 (73.2)
Purepac:fed (B)	33.922 (83)	40.234(88)	7.07936 (80.2)	2.478 (45.3)
Merck & Co.:fed (C)	37.340 (80)	39.648(85)	8.67608 (64.9)	1.783 (45.4)
Least-Squares Means				
Purepac:fast (A)	56.318	61.402	3.47797	
Purepac:fed (B)	34.047	36.662	7.04292	
Merck & Co.:fed (C)	37.395	39.192	8.69244	
Ratio of Least-Squares Means				
(B/A)%	60.5	59.7	202.5	
(B/C)%	91.0	93.5	81.0	

APPEARS THIS WAY ON ORIGINAL

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Treatment A = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fasting
Treatment B = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fed
Treatment C = Mevacor® 40 mg tablet, Dose Administered = 40 mg, fed

Table 4. FED/FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY #992517
ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS
FOR Beta-HYDROXYLOVASTATIN IN 23 SUBJECTS

PK PARAMETER	N	TEST TREATMENT A		N	TEST TREATMENT B		N	REFERENCE TREATMENT C		RATIO (B/A)%	RATIO (B/C)%
AUCT [ng•hr/mL]	23	47.80	(53.7)	23	38.62	(44.0)	23	38.58	(93.3)	80.8	100.1
Cmax [ng/mL]	23	3.4786	(48.8)	23	8.1353	(50.3)	23	7.6121	(115.9)	233.9	106.9
Tmax [hr]	23	4.913	(41.1)	23	4.241	(19.4)	23	4.000	(23.5)	86.3	106.0
AUCinf [ng•hr/mL]	18	57.40	(52.2)	12	38.76	(38.2)	14	34.91	(39.1)	67.5	111.0
kel [1/h]	18	0.08045	(52.0)	12	0.19456	(75.1)	14	0.11514	(85.5)	241.8	169.0
half-life [h]	18	12.575	(89.1)	12	7.857	(89.8)	14	10.320	(65.2)	62.5	76.1

LEAST-SQUARES MEANS FOR PHARMACOKINETIC PARAMETERS
Beta-HYDROXYLOVASTATIN, N=23*

	ln AUC_{0-t}* ng·h/mL (%CV)	lnAUC_{0-inf}* ng.h/mL (%CV)	ln C_{max}* ng/mL (%CV)	T_{max} h (%CV)
Mean				
Purepac:fast (A)	42.593 (50.4)	51.604(48)	3.08312 (55.5)	4.913 (41.1)
Purepac:fed (B)	35.471 (43.6)	36.763(33)	7.16638 (56.5)	4.241 (19.4)
Merck & Co.:fed (C)	32.231 (54.8)	32.886(36)	6.05659 (60.0)	4.000 (23.5)
Least-Squares Means				
Purepac:fast (A)	42.696	49.426	3.07549	
Purepac:fed (B)	35.132	37.980	7.08219	
Merck & Co.:fed (C)	31.806	32.023	5.98420	
Ratio of Least-Squares Means				
(B/A)%	82.3	76.8	230.3	
(B/C)%	110.5	118.6	118.3	

APPEARS THIS WAY ON ORIGINAL

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Treatment A = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fasting
Treatment B = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fed
Treatment C = Mevacor® 40 mg tablet, Dose Administered = 40 mg, fed

JUN 5 2000

BIOEQUIVALENCY DEFICIENCIES

ANDA: 75828 APPLICANT: Purepac

DRUG PRODUCT: Lovastatin Tablets, USP
10 mg, 20 mg, 40 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Fasting and non-fasting studies: You are requested to calculate elimination rate constant, AUC_{0-inf}, and elimination half-life of lovastatin as well as beta-hydroxylovastatin. Please include these data with other pharmacokinetic parameters and submit the revised data files.

2. Fasting and non-fasting studies: Please submit linear plots of individual subject plasma profiles for lovastatin and beta-hydroxylovastatin.

APPEARS THIS WAY
ON ORIGINAL

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75828
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Dhariwal /S/ 5/15/00 /S/ 5/16/00
HFD-655/Nerurkar
HFD-617/J. Fan /S/ 5/31/00
HFD-650/Dale Conner /S/ 5/31/2000

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BIOEQUIVALENCY - DEFICIENCIES Submission Date: March 29, 2000

1. **FASTING STUDY** (STF)
Clinical:
Analytical:
Strengths: 40 mg
Outcome: AC (IC) UN NC

2. **FOOD STUDY** (STP)
Clinical:
Analytical:
Strengths: 40 mg
Outcome: AC (IC) UN NC

3. **DISSOLUTION WAIVER** (DIW)
Strengths: 20 mg
Outcome: IC

4. **DISSOLUTION WAIVER** (DIW)
Strengths: 10 mg
Outcome: IC

Outcome Decisions:
IC - Incomplete

WinBio Comments

APPEARS THIS WAY ON ORIGINAL

LOVASTATIN TABLETS, USP
10 mg, 20 mg, 40 mg
ANDA 75-828
Reviewer: Kuldeep R. Dhariwal
V:\FIRMSNZ\PUREPAC\LTRS&REV\75828sdw.300

Purepac Pharmaceutical Co.
2000 Elmora Avenue
Elizabeth, NJ 07207
Submission Date: 03/29/00

Review of Bioequivalence Studies, Dissolution Data and Waiver Requests (Electronic Submission)

Introduction

Indication: Cholesterol lowering agent
Type of Submission: Original submission
Contents of Submission:
40 mg lovastatin tablets: Dissolution data and *in vivo* bioequivalence studies measuring lovastatin and metabolite, beta-hydroxylovastatin under fasting and non-fasting conditions.
10 mg and 20 mg lovastatin tablets: Dissolution data and waiver requests for *in vivo* bioequivalence study requirements.
RLD: Mevacor® tablets (Merck). The Orange Book lists 40 mg strength as RLD.
Recommended Dose: The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 10-80 mg/day in single or two divided doses; the maximum recommended dose is 80 mg/day. Doses should be individualized according to the recommended goal of therapy and the patient's response.

Background

Lovastatin is a cholesterol lowering agent. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding beta-hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.
Following an oral dose of ^{14}C-labeled lovastatin in man, 10% of the dose was excreted in urine and 83% in faeces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (lovastatin plus ^{14}C-metabolites) peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours post-dose. Lovastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of lovastatin, the availability of drug to the general circulation is low and variable.

Protocol No.: PRACS P99-370, Bioequivalence Study Under Fasting Conditions

Study Information

Clinical Facility:	[redacted]
Principal Investigator:	[redacted]
Sub-Investigator:	[redacted]
Clinical Study Dates:	Period I 08/29/99 to 09/01/99 Period II 09/12/99 to 09/15/99 Period III 09/26/99 to 09/29/99 Period IV 10/10/99 to 10/13/99
Analytical Facility	[redacted]
Analytical Section Head:	[redacted]
Analytical Study Dates:	10/20/99 to 11/22/99
Storage Period:	83 days

Treatment Information

Treatment ID:	A	B
Test or Reference:	Test	Reference
Product Name:	Lovastatin Tablets	Mevacor®
Manufacturer:	Purepac Pharmaceutical Co.	Merck & Co., Inc.
Manufacture Date:	July 22, 1999	N/A
Expiration Date:	N/A	4/00
ANDA Batch Size:	[redacted]	N/A
Batch/Lot Number:	PI-1127	H2782
Potency:	101.6%	98.1%
Content Uniformity:	101.3% (100.0-103.0%)	96.8% (94.7-98.6%)
Strength:	40 mg	40 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	40 mg	40 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight
Housing:	From 14 hours prior to dosing until 24 hours after dosing. The subjects returned for 32, 38, 48, 62, and 72 h blood draws.	

RANDOMIZATION		**DESIGN**	
Randomized:	Y	Design Type:	Crossover
No. of Sequences:	2	Replicated Treatment Design:	Y
No. of Periods:	4	Balanced:	N
No. of Treatments:	2	Washout Period:	14 days

Randomization scheme:
BAAB: 1,2,3,4,8,10,13,16,18,21,22,23,25,27,30,31,32,34,35,40,41,42,43,44
ABBA: 5,6,7,9,11,12,14,15,17,19,20,24,26,28,29,33,36,37,38,39,45,46,47,48
Subject #39 did not complete the study.

DOSING		**SUBJECTS**	
Single or Multiple Dose:	Single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	48
Route of Administration:	Oral	No. of Subjects Completing:	47
		No. of Subjects Plasma Analyzed:	47
Number of Doses:	N/A	No. of Dropouts:	1
		Sex(es) Included:	Male
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	55

Dietary Restrictions:	No caffeine and/or xanthine-containing products or alcohol 48hrs pre-dose & during sample collection. No grapefruit products 7days pre-dose & entire study. No fluid 1 hour pre- & post-dose. Subjects fasted overnight & 4hrs post-dose.
Activity Restrictions:	Subjects remained in an upright or supine position 4 hours post-dose. Only non-strenuous activity was permitted during confinement.
Drug Restrictions:	No systemic prescription medication 14 days pre-study. No investigational drugs or drugs known to induce/inhibit hepatic drug metabolism 30 days pre-study. No non-prescription medication 3 days pre-study.
Blood Sampling:	Before dosing (time 0) and at 0.25, 0.50, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 32, 38, 48, 62, and 72 hours post-dose. Blood samples were collected in EDTA vacutainers.

Study Results

1) Clinical

Adverse Events: Twenty-four subjects experienced fifty-five adverse events, out of which five were either probably or possibly related to study medication. The other fifty events were either remotely related to or unrelated to study medication. None of the events were considered serious in nature.

Subject	Complaint	Treatment	Relationship
39	Abdominal pain	Reference	Remote
43	Left knee pain	Reference	Unrelated
19	Sprain right ankle	Test	Unrelated
41	Sore lower back	Test	Unrelated
08	Bee sting	Test	Unrelated
07	Cough	Ref & Test	Unrelated

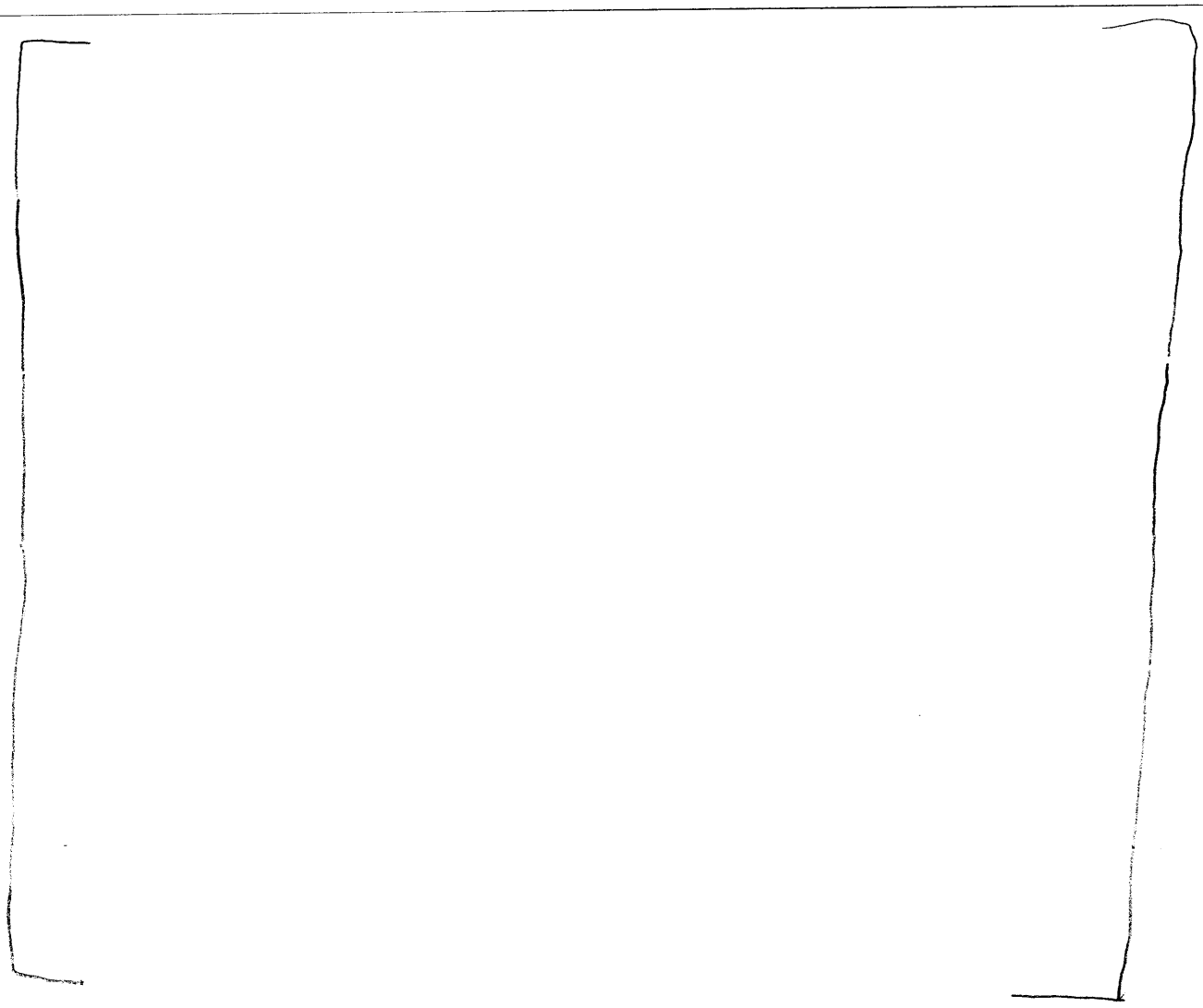
13	Cough	Test	Unrelated
15	Cough	Reference	Remote
16, 27, 43	Cough	Test	Unrelated
26	Dizziness	Reference	Unrelated
45	Fever	Test	Unrelated
1, 7, 8	Headache	Reference	Unrelated
2	Headache	Test/Ref	Remote
12, 20, 23	Headache	Test	Remote
24	Headache	Test/Ref	Possible
27, 45	Headache	Test	Remote
35	Headache	Reference	Remote
47	Headache	Reference	Probable
24	Elevated liver enzymes	Test	Remote
7, 24	Head cold	Reference	Unrelated
29	Pulled hamstring right leg	Reference	Unrelated
26	Nausea	Reference	Unrelated
4	Neck pain	Test	Unrelated
23	Sore throat	Reference	Unrelated
14, 20	Bruce right antecubital space	Test	Unrelated
15	Congested chest	Test	Unrelated
7	Head congestion	Test/Ref	Unrelated
7	Rhinitis	Test	Possible
43	Stuffy Head	Test	Test

Protocol Deviations: There were some sampling time deviations. Actual sampling times were used for pharmacokinetic calculations. Some subjects took acetaminophen, ibuprofen, Vicks DayQuil Liquicaps, Robitussin syrup, Aleve and multivitamins during the course of the study.

Dropouts:

SUBJECT NO.:	39
REASON:	personal reason (family funeral)
PERIOD:	2
REPLACEMENT:	N

2) Analytical (Not to be Released Under FOI)



3) Pharmacokinetic:

All pharmacokinetic parameters and statistical analyses reported in this review are based on firm's calculations. The reviewer has not recalculated the parameters (see comments).

Lovastatin:

Mean Plasma Concentrations:	Table 1 and Figure 1
Pharmacokinetic Parameters:	Table 2
90% Confidence Intervals:	Table 2

Beta-Hydroxylovastatin:

Mean Plasma Concentrations:	Table 3 and Figure 2
Pharmacokinetic Parameters:	Table 4

90% Confidence Intervals: Table 4

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4) Statistical Analysis:

1. Arithmetic means and least squares means were calculated for AUC_{0-t} and C_{max}.
2. ANOVA were performed on log transformed AUC_{0-t} and C_{max}. The first analyses of variance model included drug formulation, period, first-order carryover, sequence, form*subject nested within sequence and subject nested within sequence as factors. A 5% level of significance was used for all the comparisons (period, formulation, sequence, carryover). The carryover was not statistically significant and was therefore dropped from the model for the final analyses.

Comments:

1. The protocol states that the analyte concentration-time data will be used to calculate the pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, elimination rate constant and elimination half-life. The firm, however, did not calculate AUC_{0-inf}, elimination rate constant and elimination half-life of lovastatin and its metabolite. The firm states that due to the hepatic recycling observed with lovastatin and beta-hydroxylovastatin, the absorption and the elimination of the drug and metabolite occur simultaneously and therefore the calculation of the elimination constant is of no pharmacokinetic significance.
2. **NOT TO BE RELEASED UNDER FOI:** [redacted]
3. The individual subject plasma profiles (semi-log plots) suggest that the elimination rate constant can be calculated for many subjects.
4. The firm would be requested to calculate elimination rate constant, AUC_{0-inf}, and elimination half-life of lovastatin as well as beta-hydroxylovastatin. The reviewer will perform the statistical analyses of the data after receiving the requested data.
5. The firm has also performed statistical analyses to assess individual bioequivalence. The individual bioequivalence guidance is in the draft form and therefore the individual bioequivalence results can not be used for regulatory decisions.

Conclusion:

The fasting study is incomplete.

Protocol No.: PRACS P99-410, A Limited Food Effects Study of 40 mg Lovastatin Tablets

Study Information

Clinical Facility:	[redacted]
Medical Director:	[redacted]
Sub Investigator:	[redacted]

Clinical Study Dates:	Period I 12/04/99 to 12/07/99 Period II 12/11/99 to 12/14/99 Period III 12/18/99 to 12/21/99
Analytical Facility	[redacted]
Analytical Program Manager:	[redacted]
Analytical Study Dates:	01/03/00 to 01/20/00
Storage Period:	46 days

TREATMENT INFORMATION

Treatment ID:	A	B	C
Test or Reference:	T	T	R
Product Name:	Lovastatin Tablets	Lovastatin Tablets	Mevacor®
Manufacturer:	Purepac Pharmaceutical Co.	Purepac Pharmaceutical Co.	Merck & Co., Inc.
Batch/Lot Number:	PI-1127	PI-1127	H2782
Strength:	40 mg	40 mg	40 mg
Dosage Form:	Tablet	Tablet	Tablet
Dose Administered:	40 mg	40 mg	40 mg
Study Condition:	Fasting	Fed	Fed
Length of Fasting:	Overnight	Overnight	Overnight
Food-Drug Interval:	N/A	30 minutes	30 minutes
Standardized Breakfast:	N/A	Y	Y
Breakfast Specifics:	N/A	One buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, 180 mL orange juice, 240 mL whole milk	One buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, 180 mL orange juice, 240 mL whole milk

Randomization		**Design**	
Randomized:	Y	Design Type:	crossover
No. of Sequences:	6	Replicated Treatment Design:	N
No. of Periods:	3	Balanced:	N
No. of Treatments:	3	Washout Period:	7 days

Randomization Scheme:
ABC: 1, 17, 20, 21
CBA: 2, 6, 8, 18
BCA: 3, 7, 14, 19
CAB: 4, 9, 13, 15
ACB: 5, 11, 12, 23
BAC: 10, 16, 22, 24
Subject #14 did not complete the study.

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ON ORIGINAL

Dosing		Subjects	
Single or Multiple Dose:	single	IRB Approval:	Y
Steady State:	N	Informed Consent Obtained:	Y
Volume of Liquid Intake:	240 mL	No. of Subjects Enrolled:	24
Route of Administration:	oral	No. of Subjects Completing:	23
		No. of Subjects Plasma Analyzed:	23
Number of Doses:	N/A	No. of Dropouts:	1
		Sex(es) Included:	male
Steady State Dose Time:	N/A	Healthy Volunteers Only:	Y
Length of Infusion:	N/A	No. of Adverse Events:	49
Blood Sampling:	Same as in fasting study		

Study Results

1) Clinical

Adverse Events: Of the forty-nine adverse events, three were either probably or possibly related to study medication. The other forty-six adverse events were either remotely related to or unrelated to study medication. Subject #1 reported vomiting (2x) approximately 50 and 55 hours after period II dose (test fed) administration. Subject #17 reported vomiting (2x) approximately 36 and 37.5 hours after period II dose (test fed) administration. Since all episodes of the vomiting occurred well after the C_{max} of lovastatin and its metabolite, these subjects need not be omitted from the analyses.

Subject No.	Event	Relationship To Study Drug	Study Drug
07	Back Pain (Lower Back Pain)	4	A
06	Cold and Hot Flashes	3	A
22	Coughing (Cough)	4	A
06	Diarrhea	3	A
17	Diarrhea	4	B
01	Dyspepsia (Stomach Upset)	4	B
17	Fatigue (Tired)	4	B
02	Headache	4	C
03	Headache	3	B
03	Headache	3	A
06	Headache	1	A
11	Headache	1	C
20	Headache	4	B
20	Headache	3	C
21	Headache	3	A
22	Headache	4	A
24	Headache	4	A
22	Laceration (Cut Right Index Finger)	4	B
15	Left Sore Elbow	4	A
20	Malaise	4	C
17	Malaise (Body Aches)	4	B
21	Malaise (Body Aches)	3	A

Subject No.	Event	Relationship To Study Drug	Study Drug
01	Malaise (Head Cold)	4	B
23	Malaise (Head Cold)	4	A
13	Mouth Dry (Dry Throat)	3	A
06	Nausea	3	A
17	Nausea (Nausea)	4	B
18	Nausea (Nauseous)	4	B
24	Pallor	4	A
02	Pharyngitis (Sore Throat)	4	C
10	Pharyngitis (Sore Throat)	3	B
14	Pharyngitis (Sore Throat)	4	B
21	Pharyngitis (Sore Throat)	3	A
22	Pharyngitis (Sore Throat)	4	A
10	Purpura (Hematoma Left Arm Antecubital Space)	4	A
02	Purpura (Hematoma Right Arm Antecubital Space)	4	C
01	Rhinitis (Runny Nose)	2	A
09	Rhinitis (Runny Nose)	4	A
14	Rhinitis (Stuffy Nose)	4	B
20	Rhinitis (Stuffy Nose)	4	A
01	Sore Right Leg	4	A
14	Strep Throat	4	B
07	Tooth Pain (Upper Left Front Tooth Pain)	4	B
07	Tooth Pain (Upper Left Front Tooth Pain)	4	B
07	Tooth Pain (Upper Left Front Tooth Pain)	4	B
01	Vomiting (Vomited)	4	B
01	Vomiting (Vomited)	4	B
17	Vomiting (Vomiting)	4	B
17	Vomiting (Vomiting)	4	B

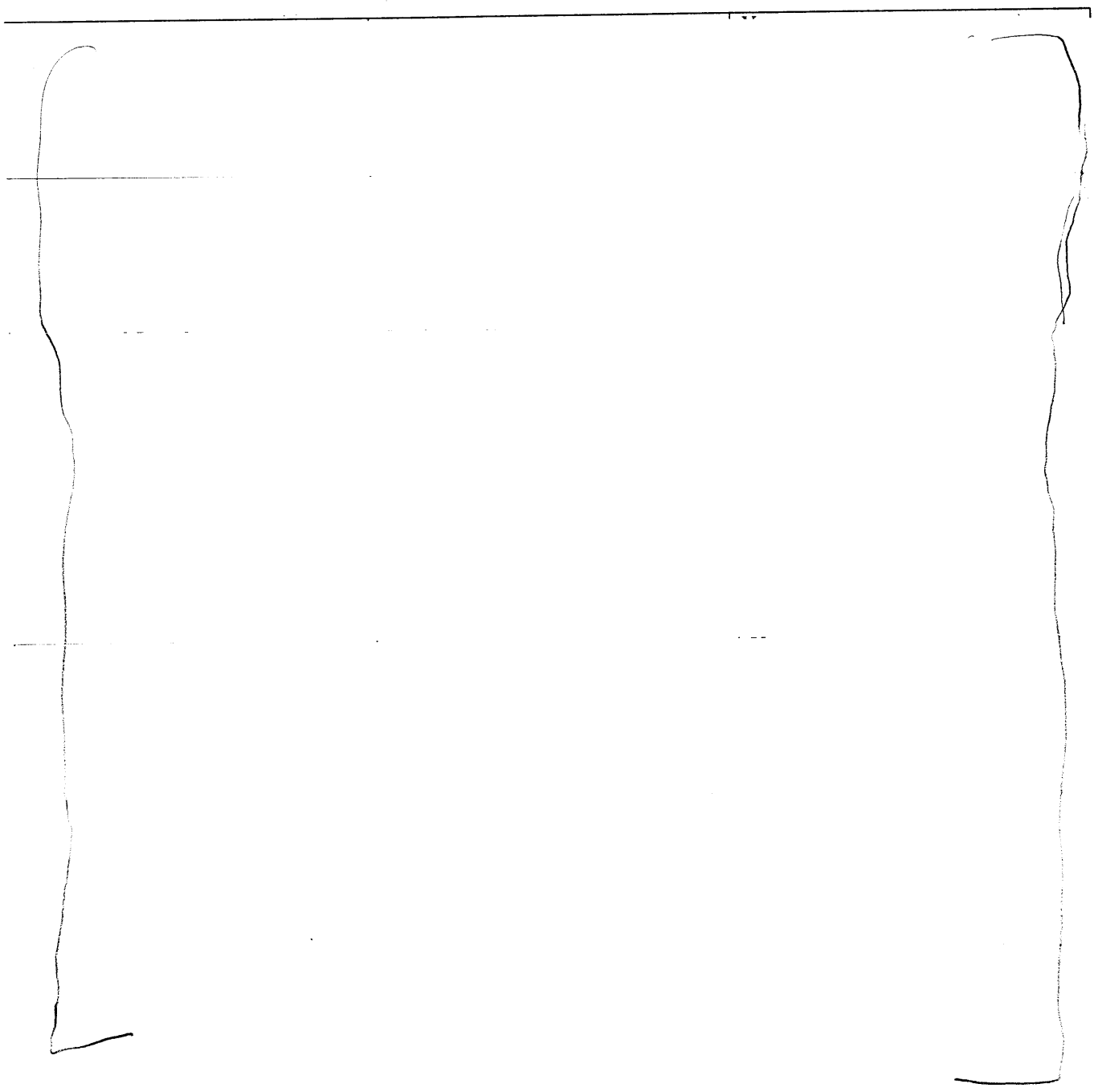
Legend: Relationship to Study Drug: 1=Probable; 2=Possible; 3=Remote; 4=Unrelated

Study Drug: A (fasting) = Lovastatin Tablets, USP [Purepac Pharmaceutical Co.]
B (fed) = Lovastatin Tablets, USP [Purepac Pharmaceutical Co.]
C (fed) = Mevacor® Tablets [MERCK & CO., INC.]

Protocol Deviations: Some subjects took ibuprofen, Imodium chewable tablets, Phenergan and Tylenol during the course of the study. There were some sampling time deviations. Actual sampling times were used for pharmacokinetic calculations.

Dropouts: Subject #14 was dropped prior to period II dosing secondary to an illness (strep throat) requiring therapy with Azithromycin.

2) Analytical (Not to be Released Under FOI)



3) Pharmacokinetic:

All pharmacokinetic parameters and statistical analyses reported in this review are based on firm's calculations. The reviewer has not recalculated the parameters (see comments).

Lovastatin:

Mean Plasma Concentrations:	Table 5, Figure 3
Pharmacokinetic Parameters:	Table 6
Ratio of Means:	Table 6

Beta-Hydroxylovastatin:
Mean Plasma Concentrations: Table 7, Figure 4
Pharmacokinetic Parameters: Table 8
Ratio of Means: Table 8
4) Statistical Analysis:

Arithmetic means, geometric means, and least squares means were calculated for AUC_{0-t}, C_{max}, and T_{max}. Ratios of means were calculated using the LSM for both ln-transformed and untransformed AUC_{0-t} and C_{max}.

Comments:

1. The protocol states that the analyte concentration-time data will be used to calculate the pharmacokinetic parameters: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, elimination rate constant and elimination half-life. The firm, however, did not calculate AUC_{0-inf}, elimination rate constant and elimination half-life of lovastatin and its metabolite. The firm states that due to the hepatic recycling observed with lovastatin and beta-hydroxylovastatin, the absorption and the elimination of the drug and metabolite occur simultaneously and therefore the calculation of the elimination constant is of no pharmacokinetic significance.
2. **NOT TO BE RELEASED UNDER FOI**:
3. The individual subject plasma profiles (semi-log plots) suggest that the elimination rate constant can be calculated for many subjects.
4. The firm would be requested to calculate elimination rate constant, AUC_{0-inf}, and elimination half-life of lovastatin as well as beta-hydroxylovastatin. The reviewer will perform the statistical analyses of the data after receiving the requested data.

Conclusion: The non-fasting study is incomplete.

Formulation (Not to be released under FOI)

Ingredient	Strength 10 mg	Strength 20 mg	Strength 40 mg
LOVASTATIN USP	10 mg	20 mg	40 mg
Microcrystalline Cellulose			
Lactose Monohydrate NF			
Pregelatinized Starch NF,			
Butylated Hydroxyanisole			
Magnesium Stearate NF			
D&C Red #30 Aluminum Lake,			

D&C Yellow #10 HT Aluminum Lake,			
TOTAL TABLET WEIGHT	**210 mg**	**210 mg**	**210 mg**

Test tablets: **10 mg**: White, round flat faced, beveled edge tablets, imprinted with Purepac logo 'R' on one side and '633' on the other side; **20 mg**: Pink, round flat faced, beveled edge tablets, imprinted with Purepac logo 'R' on one side and '634' on the other side; **40 mg:** Yellow, round flat faced, beveled edge tablets, imprinted with Purepac logo 'R' on one side and '635' on the other side.

Reference tablets: **10 mg:** Peach, octagonal tablets, coded MSD 730 on one side and MEVACOR on the other; **20 mg:** Light blue, octagonal tablets, coded MSD 731 on one side and MEVACOR on the other; **40 mg:**Green, octagonal tablets, coded MSD 732 on one side and MEVACOR on the other.

Formulation Comments:

1. All inactive ingredients are within approved safety limits (FDA Inactive Ingredient Guide, January 1996).
2. The three strengths of the test tablets have identical weights. The three strengths of the reference listed drug do not appear to have identical weights (page 323, PDR 2000).

Dissolution and Waiver Request:

IN VITRO DISSOLUTION TESTING

Test Drug: Lovastatin USP tablets manufactured by Purepac
Reference Drug: Mevacor® tablets manufactured by Merck & Co.
Dose Strength: 10 mg

I. Conditions for Dissolution/Release Testing: USP method

Tolerance: NLT (Q) in 30 minutes

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (min)	Test Product Lot No.: PI-1123			Reference Product Lot No.: J1078		
	Mean %	Range	% CV	Mean %	Range	% CV
10	97.27		0.9	83.73		2.82
20	98.68		0.83	92.88		1.00
30	98.73		0.63	94.98		1.13
45	98.72		0.69	95.99		1.13

Test Drug: Lovastatin USP tablets manufactured by Purepac
Reference Drug: Mevacor® tablets manufactured by Merck & Co.
Dose Strength: 20 mg

I. Conditions for Dissolution/Release Testing: Same as for 10 mg strength

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (min)	Test Product Lot No.: PI-1125			Reference Product Lot No.: J1034		
	Mean %	Range	% CV	Mean %	Range	% CV
10	99.49		1.64	86.31		2.63
20	100.94		1.64	92.93		1.63
30	100.7		1.1	94.74		1.5

45	100.5	99.3-102.7	1.1	95.73	93.3-98.0	1.5

Test Drug: Lovastatin USP tablets manufactured by Purepac
Reference Drug: Mevacor® tablets manufactured by Merck & Co.
Dose Strength: 40 mg

I. Conditions for Dissolution/Release Testing: Same as for 10 mg strength

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times (min)	Test Product Lot No.: PI-1127			Reference Product Lot No.: H2782		
	Mean %	Range	% CV	Mean %	Range	% CV
10	99.63		1.3	93.63		1.95
20	101.79		1.33	96.2		1.93
30	101.14		1.45	96.14		1.88
45	100.55		0.87	96.53		1.70

F2 factor across test and reference products

Strength	Test vs. Reference
10 mg	55.43
20 mg	53.13
[1]40 mg	63.78

f2 factor across different strengths

Product	[1]40 mg vs 10 mg	[1]40 mg vs 20 mg
Test	78.72	97.71
Reference	63.57	68.79

[1]Used in the *in vivo* studies.

Comments:

1. The dissolution testing was carried out as per USP 24. All strengths of the test product meet the USP specification of NLT — (Q) in 30 minutes.
2. The similarity factor (f_2) is between 50 and 100 for all dissolution profile comparisons. This suggests that dissolution profiles of 10 and 20 mg strengths of the test product are similar to the 40 mg strength used in the *in vivo* studies and all three strengths of the test product are similar to the respective strengths of the reference product.
3. The 10 and 20 mg test tablets are proportionally similar in their active and inactive ingredients to the 40 mg tablet.

Deficiencies:

1. Fasting and non-fasting studies: The firm has not calculated elimination rate constant, AUC_{0-inf}, and elimination half-life of lovastatin as well as beta-hydroxylovastatin. The firm should include these data with other pharmacokinetic parameters in its data files and submit the revised data files.
2. Fasting and non-fasting studies: The firm has not submitted linear plots of individual subject plasma profiles for lovastatin and beta-hydroxylovastatin.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Purepac on its lovastatin 40 mg tablet, lot #PI-1127 comparing it to Mevacor® 40 mg tablet, lot #H2782 manufactured by Merck is incomplete.
2. The bioequivalence study conducted under non-fasting conditions by Purepac on its lovastatin 40 mg tablet, lot #PI-1127 comparing it to Mevacor® 40 mg tablet, lot #H2782 manufactured by Merck is incomplete.
3. The dissolution testing conducted by the firm on its lovastatin 10 mg, 20 mg, and 40 mg tablets is acceptable. The formulation for 10 mg and 20 mg test tablets is proportionally similar to the 40 mg strength of the test product which underwent bioequivalence testing. The waiver of the *in vivo* bioequivalence study requirements for 10 mg and 20 mg test tablets is denied pending approval of 40 mg test tablets.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

/S/ Date 5/16/2000

Concur: /S/ Date 5/31/2000

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY ON ORIGINAL

Table 1. Mean Plasma Concentrations of LOVASTATIN, N=47
Treatment A = Lovastatin 40 mg tablet, Dose Administered = 1x40 mg, fasting
Treatment B = Mevacor® 40 mg tablet, Dose Administered = 1x40 mg, fasting

Plasma Concentration Data File PUR0001.eaa

Time(hours)	Test Mean	Test %CV	Ref Mean	Ref %CV	T/R Ratio
	(A)	(A)	(B)	(B)	(A)/(B)
0	0.	0.	0.	0.	**
0.25	0.12	162.57	0.13	158.63	0.951
0.5	0.69	97.83	0.67	94.33	1.039
1	1.37	65.68	1.28	71.51	1.065
1.5	1.64	61.24	1.48	62.85	1.107
2	1.81	69.47	1.73	86.88	1.046
2.5	1.74	66.61	1.78	87.8	0.975
3	1.64	67.9	1.74	90.37	0.941
3.5	1.57	66.77	1.61	91.99	0.977
4	1.47	65.64	1.54	93.92	0.95
4.5	1.75	65.75	1.81	97.8	0.965
5	2.54	61.68	2.5	76.33	1.014
6	2.42	68.12	2.37	89.55	1.023
8	1.48	74.09	1.39	83.13	1.067
10	1.53	74.84	1.36	75.97	1.122
12	1.43	77.89	1.32	84.8	1.088
16	1.34	81.91	1.1	82.29	1.222
24	1.15	91.82	0.98	92.72	1.171
32	0.64	83.57	0.55	77.27	1.152
38	0.34	95.5	0.27	91.89	1.272
48	0.11	137.52	0.09	134.95	1.209
62	0.02	289.89	0.01	348.27	1.705
72	0.01	570.72	0.00	0.00	**

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Table 2. Lovastatin Pharmacokinetic Parameters: Least-Squares Means*, N=47
Treatment A = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fasting
Treatment B = Mevacor® 40 mg tablet, Dose Administered = 40 mg, fasting

	ln AUC_{0-t}[1] ng.h/mL (%CV)	ln C_{max}[1] ng/mL (%CV)	T_{max} Hour (%CV)
Mean			
Purepac (A)	39.438 (66.1)	2.6765 (59.6)	4.894 (68.2)
Merck&Co (B)	34.529 (68.9)	2.6120 (70.8)	5.660(104.1)
Least-Squares Means			
Purepac (A)	39.4545	2.67776	
Merck&Co (B)	34.5864	2.61501	
Ratio of Least-Squares Means (A/B)%	114.1	102.4	
90% Confidence Intervals (A/B)%			
Lower limit:	107.3	94.9	
Upper limit:	121.3	110.5	
p-value (ANOVA)			
A vs B	0.0007	0.6036	
Period	0.0135	0.0188	
Sequence	0.5536	0.6272	
Intrasubject CV%	33.1	32.7	

1. For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Arithmetic Means*			
Parameter	A	B	Ratio
AUC_{0-t}	47.330	41.914	1.129
C_{max}	3.103	3.231	0.960
T_{max}	4.894	5.66	

* As reported by the firm

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Table 3. Mean Plasma Concentrations of Beta-HYDROXYLOVASTATIN, N=47
Treatment A = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fasting
Treatment B = Mevacor® 40 mg tablet, Dose Administered = 40 mg, fasting

Plasma Concentration Data File PUR0001.eab

Time(hours)	Test Mean	Test %CV	Ref Mean	Ref %CV	T/R Ratio
	(A)	(A)	(B)	(B)	(A)/(B)
0	0.0	0.0	0.0	0.0	**
0.25	0.0	969.54	0.02	253.52	0.066
0.5	0.09	115.11	0.14	114.48	0.638
1	0.45	81.9	0.53	90.12	0.846
1.5	0.88	83.62	0.96	83.83	0.917
2	1.34	76.14	1.47	78.77	0.909
2.5	1.72	72.18	1.89	75.39	0.911
3	1.98	73.3	2.15	69.65	0.92
3.5	2.21	68.51	2.38	67.72	0.928
4	2.37	64.15	2.52	66.00	0.94
4.5	2.63	57.61	2.78	61.77	0.946
5	2.08	51.71	2.15	54.96	0.968
6	1.45	49.21	1.5	57.22	0.967
8	1.14	53.25	1.14	61.81	1.00
10	1.09	55.33	1.05	68.92	1.031
12	0.76	74.95	0.76	85.18	1.004
16	0.81	88.43	0.72	80.46	1.124
24	0.91	89.01	0.85	89.06	1.077
32	0.65	94.65	0.65	105.04	1.004
38	0.41	100.28	0.37	117.	1.122
48	0.16	163.65	0.15	167.7	1.08
62	0.05	238.35	0.06	261.5	0.914
72	0.03	376.65	0.02	426.04	1.581

Table 4. Beta-Hydroxylovastatin Pharmacokinetic Parameters: Least Squares Means*, N=47
Treatment A = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fasting
Treatment B = Mevacor® 40 mg tablet, Dose Administered = 40 mg, fasting

	ln AUC_{0-t}[1] ng·h/mL (%CV)	ln C_{max}[1] ng/mL (%CV)	T_{max} Hour (%CV)
Mean			
Purepac (A)	33.094 (60.6)	2.4653 (50.4)	5.324 (83.0)
Merck&Co (B)	31.608 (67.4)	2.6509 (56.3)	5.288 (90.5)
Least-Squares Means			
Purepac (A)	33.1932	2.4700	
Merck&Co (B)	31.6722	2.6524	
Ratio of Least-Squares Means (A/B)%	104.8	93.1	
90% Confidence Intervals (A/B)%			
Lower limit:	98.9	86.7	
Upper limit:	111.1	100.0	
p-value (ANOVA)			
A vs B	0.1842	0.1018	
Period	0.4176	0.9655	
Sequence	0.1415	0.3697	
Intrasubject CV%	26.3	28.1	

1. For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Arithmetic Means*			
Parameter	A	B	Ratio
AUC_{0-t}	38.810	38.131	1.02
C_{max}	2.784	3.057	0.91
T_{max}	5.324	5.288	

* As reported by the firm

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Table 5

FED/FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 23 SUBJECTS
LOVASTATIN

TIME (HR)	TEST TREATMENT A		TEST TREATMENT B		TEST TREATMENT C		RATIO (B/A)%	RATIO (B/C)%
0	0.0000	(0.0)	0.0000	(0.0)	0.0000	(0.0)	N/A	N/A
0.25	0.2703	(149.5)	0.5393	(236.0)	0.6312	(203.8)	199.5	85.4
0.5	0.9459	(94.7)	1.7706	(153.3)	2.7439	(139.0)	187.2	64.5
1	1.5600	(72.3)	4.3523	(86.9)	6.7835	(79.6)	279.0	64.2
1.5	1.7744	(62.7)	5.8409	(69.5)	8.6797	(56.4)	329.2	67.3
2	1.9090	(50.4)	6.9483	(71.1)	8.8016	(58.9)	364.0	78.9
2.5	2.0509	(55.2)	6.2506	(65.2)	7.3120	(67.1)	304.8	85.5
3	1.9947	(56.7)	5.8475	(67.3)	5.9514	(79.2)	293.2	98.3
3.5	1.8418	(58.7)	5.4621	(84.5)	5.0100	(86.5)	296.6	109.0
4	1.8085	(56.9)	4.8587	(93.1)	4.2999	(91.8)	268.7	113.0
4.5	2.1924	(58.6)	4.8533	(114.8)	3.9649	(93.7)	221.4	122.4
5	3.1226	(58.8)	3.7505	(104.9)	3.3009	(95.8)	120.1	113.6
6	2.6881	(55.0)	2.1205	(106.8)	2.1382	(90.6)	78.9	99.2
8	1.9588	(58.8)	1.2045	(120.5)	1.1601	(99.8)	61.5	103.8
10	1.6608	(65.5)	1.1002	(141.6)	0.9330	(118.9)	66.2	117.9
12	2.2460	(84.2)	0.9229	(127.7)	0.9164	(122.9)	41.1	100.7
16	2.0216	(99.3)	0.5996	(146.1)	0.6121	(123.2)	29.7	98.0
24	1.8317	(94.3)	0.4163	(125.3)	0.4852	(133.0)	22.7	85.8
32	0.9046	(78.9)	0.1697	(131.3)	0.1558	(130.2)	18.8	108.9
38	0.4056	(102.9)	0.0776	(170.6)	0.0748	(140.8)	19.1	103.7
48	0.2032	(125.6)	0.0255	(276.0)	0.0301	(230.9)	12.5	84.7
62	0.0503	(214.1)	0.0000	(0.0)	0.0050	(469.0)	0.0	0.0
72	0.0131	(335.5)	0.0000	(0.0)	0.0000	(0.0)	0.0	N/A

Treatment A = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fasting
Treatment B = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fed
Treatment C = Mevacor® 40 mg tablet, Dose Administered = 40 mg, fed

Table 6

FED/FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS FOR LOVASTATIN IN 23 SUBJECTS*

PK PARAMETER	TEST TREATMENT A		TEST TREATMENT B		REFERENCE TREATMENT C		RATIO (B/A)%	RATIO (B/C)%
AUC_{0-t} [ng•hr/mL]	66.94	(67.9)	44.73	(89.9)	48.01	(80.8)	66.8	93.2
C_{max} [ng/mL]	3.7600	(44.8)	8.8168	(66.2)	10.1587	(55.8)	234.5	86.8
T_{max} [hr]	8.891	(73.2)	2.478	(45.3)	1.783	(45.4)	27.9	139.0

LEAST-SQUARES MEANS FOR PHARMACOKINETIC PARAMETERS LOVASTATIN (N=23)*

	ln AUC_{0-t}* ng·h/mL (%CV)	ln C_{max}* ng/mL (%CV)	T_{max} h (%CV)
Mean			
Purepac:fast (A)	55.420 (70)	3.46437 (42.5)	8.891 (73.2)
Purepac:fed (B)	33.922 (83.7)	7.07936 (80.2)	2.478 (45.3)
Merck & Co.:fed (C)	37.340 (80.2)	8.67608 (64.9)	1.783 (45.4)
Least-Squares Means			
Purepac:fast (A)	56.318	3.47797	
Purepac:fed (B)	34.047	7.04292	
Merck & Co.:fed (C)	37.395	8.69244	
Ratio of Least-Squares Means			
(B/A)%	60.5	202.5	
(B/C)%	91.0	81.0	

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Treatment A = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fasting
Treatment B = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fed
Treatment C = Mevacor® 40 mg tablet, Dose Administered = 40 mg, fed

* As reported by the firm

Table 7

FED/FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY
ARITHMETIC MEAN PLASMA CONCENTRATIONS [NG/ML] (CV%)
VERSUS TIME IN 23 SUBJECTS
Beta-HYDROXYLOVASTATIN

TIME (HR)	TEST TREATMENT A		TEST TREATMENT B		TEST TREATMENT C		RATIO (B/A)%	RATIO (B/C)%
0	0.0000	(0.0)	0.0000	(0.0)	0.0000	(0.0)	N/A	N/A
0.25	0.0114	(331.3)	0.0118	(327.9)	0.0170	(266.1)	103.5	69.4
0.5	0.1633	(116.3)	0.0882	(197.0)	0.1386	(132.7)	54.0	63.6
1	0.5219	(98.1)	0.5425	(76.5)	0.8311	(77.0)	103.9	65.3
1.5	0.9397	(91.0)	1.3260	(57.9)	1.9056	(63.7)	141.1	69.6
2	1.3737	(81.4)	2.4641	(49.3)	3.1591	(58.2)	179.4	78.0
2.5	1.8526	(72.0)	3.3913	(44.1)	3.8589	(57.4)	183.1	87.9
3	2.0896	(58.4)	4.2756	(42.1)	4.7190	(74.2)	204.6	90.6
3.5	2.3187	(48.1)	5.5678	(43.3)	5.4131	(83.7)	240.1	102.9
4	2.6877	(45.0)	6.4273	(49.2)	5.8628	(104.0)	239.1	109.6
4.5	3.1759	(46.3)	7.5620	(54.3)	6.5764	(92.9)	238.1	115.0
5	2.4631	(47.4)	6.5266	(57.8)	6.3197	(144.5)	265.0	103.3
6	1.7113	(44.9)	3.7675	(54.7)	4.0506	(139.2)	220.2	93.0
8	1.4194	(44.3)	1.5561	(50.3)	1.5057	(94.2)	109.6	103.3
10	1.3796	(97.1)	1.1007	(102.5)	0.9099	(86.6)	79.8	121.0
12	1.1432	(73.5)	0.7877	(117.6)	0.5866	(69.4)	68.9	134.3
16	0.8481	(98.3)	0.2613	(73.6)	0.2519	(77.0)	30.8	103.7
24	1.0769	(71.1)	0.1869	(71.4)	0.2427	(86.0)	17.4	77.0
32	0.7822	(61.2)	0.1366	(99.7)	0.1598	(92.1)	17.5	85.5
38	0.4981	(96.0)	0.0724	(150.1)	0.0674	(137.7)	14.5	107.4
48	0.2550	(136.6)	0.0364	(201.8)	0.0282	(315.3)	14.3	129.1
62	0.1117	(184.6)	0.0137	(479.6)	0.0083	(469.0)	12.3	165.1
72	0.0598	(248.1)	0.0134	(479.6)	0.0096	(479.6)	22.4	139.6

Treatment A = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fasting
Treatment B = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fed
Treatment C = Mevacor® 40 mg tablet, Dose Administered = 40 mg, fed

APPEARS THIS WAY
ON ORIGINAL

Table 8

FED/FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY ARITHMETIC MEANS (CV%) OF PHARMACOKINETIC PARAMETERS FOR Beta-HYDROXYLOVASTATIN IN 23 SUBJECTS*

PK PARAMETER	TEST TREATMENT A		TEST TREATMENT B		REFERENCE TREATMENT C		RATIO (B/A)%	RATIO (B/C)%
AUC_{0-t} [ng•hr/mL]	47.80	(53.7)	38.62	(44.0)	38.58	(93.3)	80.8	100.1
C_{max} [ng/mL]	3.4786	(48.8)	8.1353	(50.3)	7.6121	(115.9)	233.9	106.9
T_{max} [hr]	4.913	(41.1)	4.241	(19.4)	4.000	(23.5)	86.3	106.0

FED/FASTING SINGLE-DOSE IN VIVO BIOEQUIVALENCE STUDY LEAST-SQUARES MEANS FOR PHARMACOKINETIC PARAMETERS Beta-HYDROXYLOVASTATIN, N=23*

	ln AUC_{0-t}* ng·h/mL (%CV)	ln C_{max}* ng/mL (%CV)	T_{max} h (%CV)
Mean			
Purepac:fast (A)	42.593 (50.4)	3.08312 (55.5)	4.913 (41.1)
Purepac:fed (B)	35.471 (43.6)	7.16638 (56.5)	4.241 (19.4)
Merck & Co.:fed (C)	32.231 (54.8)	6.05659 (60.0)	4.000 (23.5)
Least-Squares Means			
Purepac:fast (A)	42.696	3.07549	
Purepac:fed (B)	35.132	7.08219	
Merck & Co.:fed (C)	31.806	5.98420	
Ratio of Least-Squares Means			
(B/A)%	82.3	230.3	
(B/C)%	110.5	118.3	

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.

Treatment A = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fasting
Treatment B = Lovastatin 40 mg tablet, Dose Administered = 40 mg, fed
Treatment C = Mevacor® 40 mg tablet, Dose Administered = 40 mg, fed

*** As reported by the firm**

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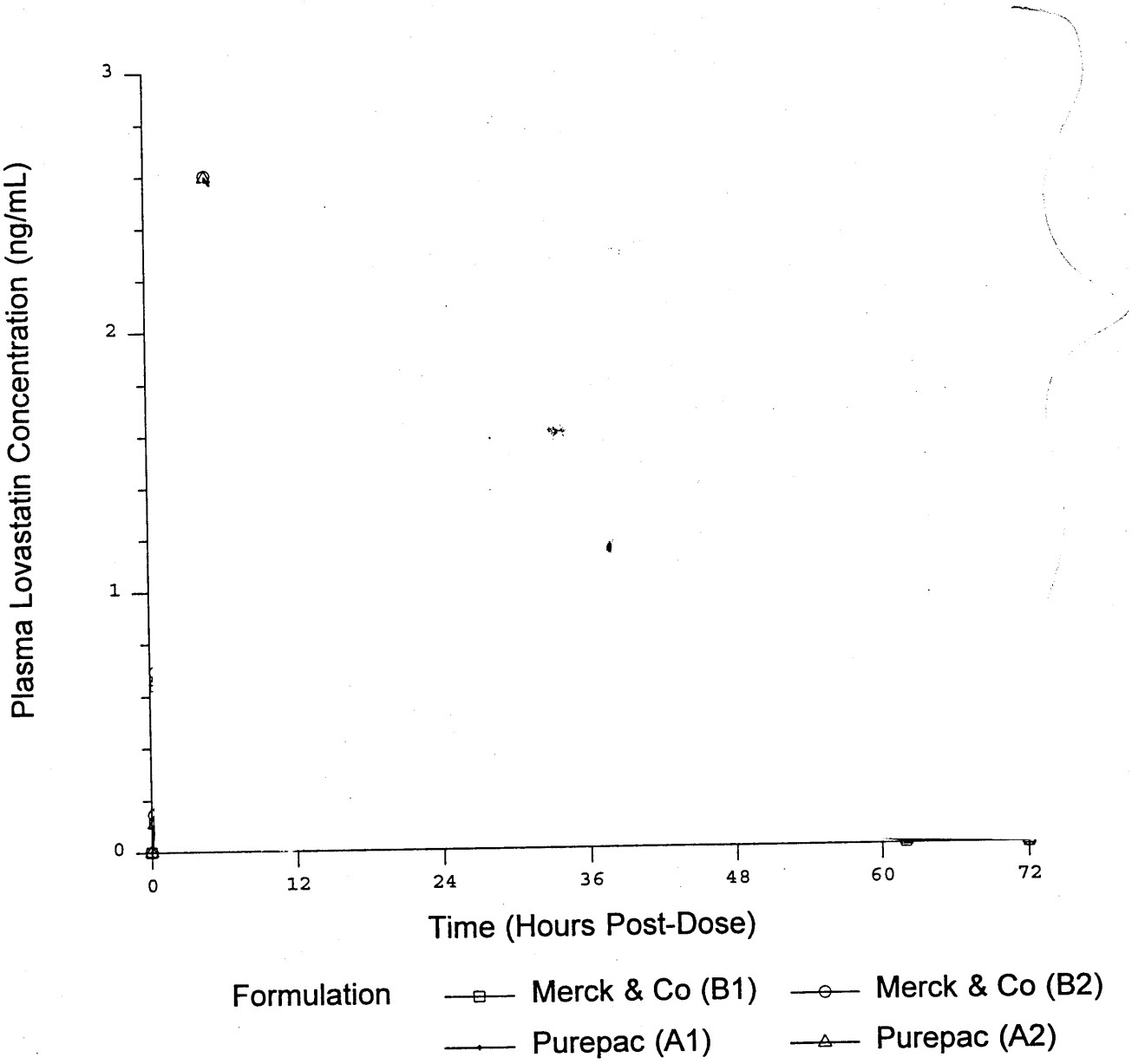
Figure 1. LOVASTATIN PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME
SINGLE-DOSE FASTING STUDY #992259

(LINEAR PLOT)



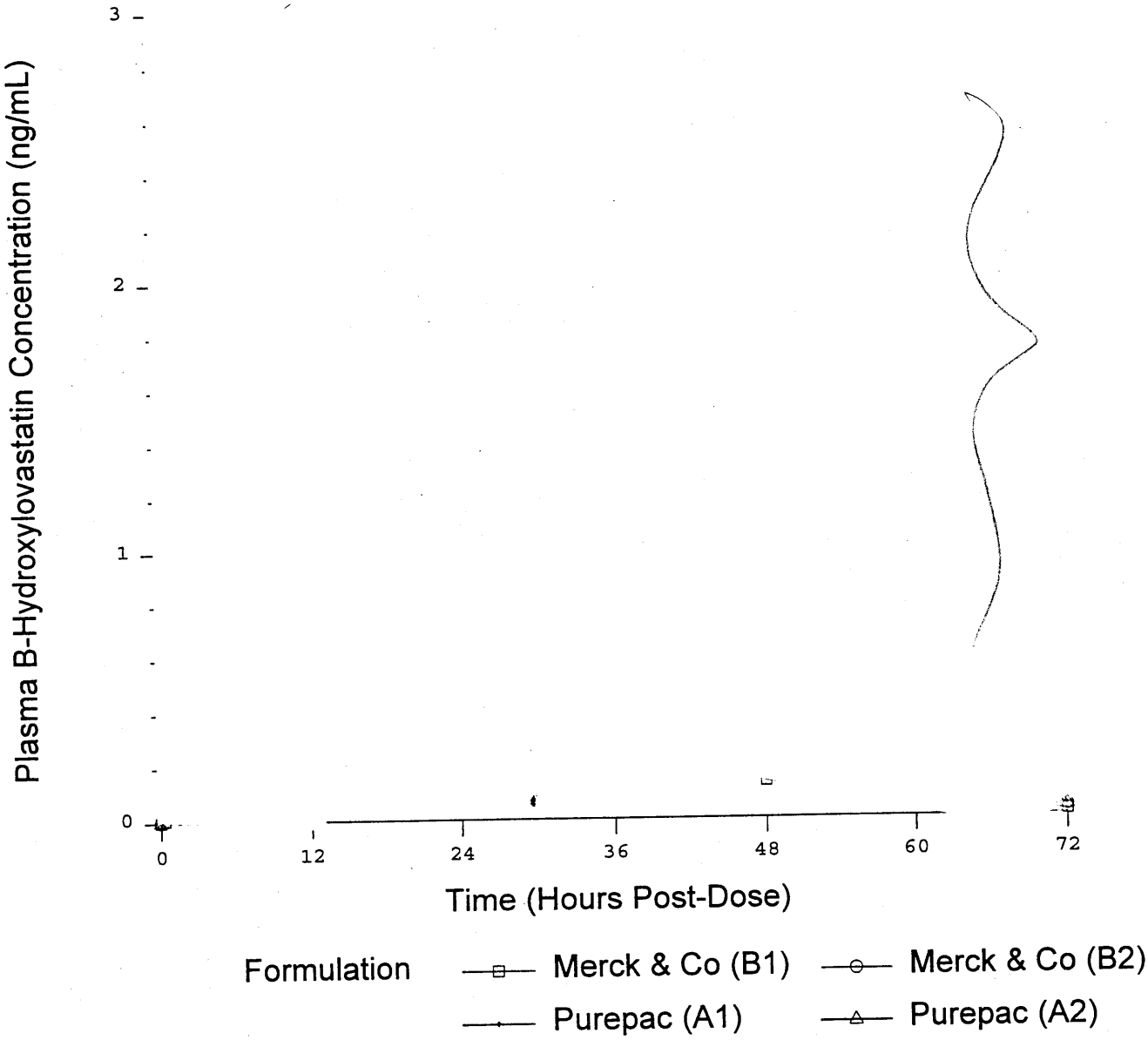
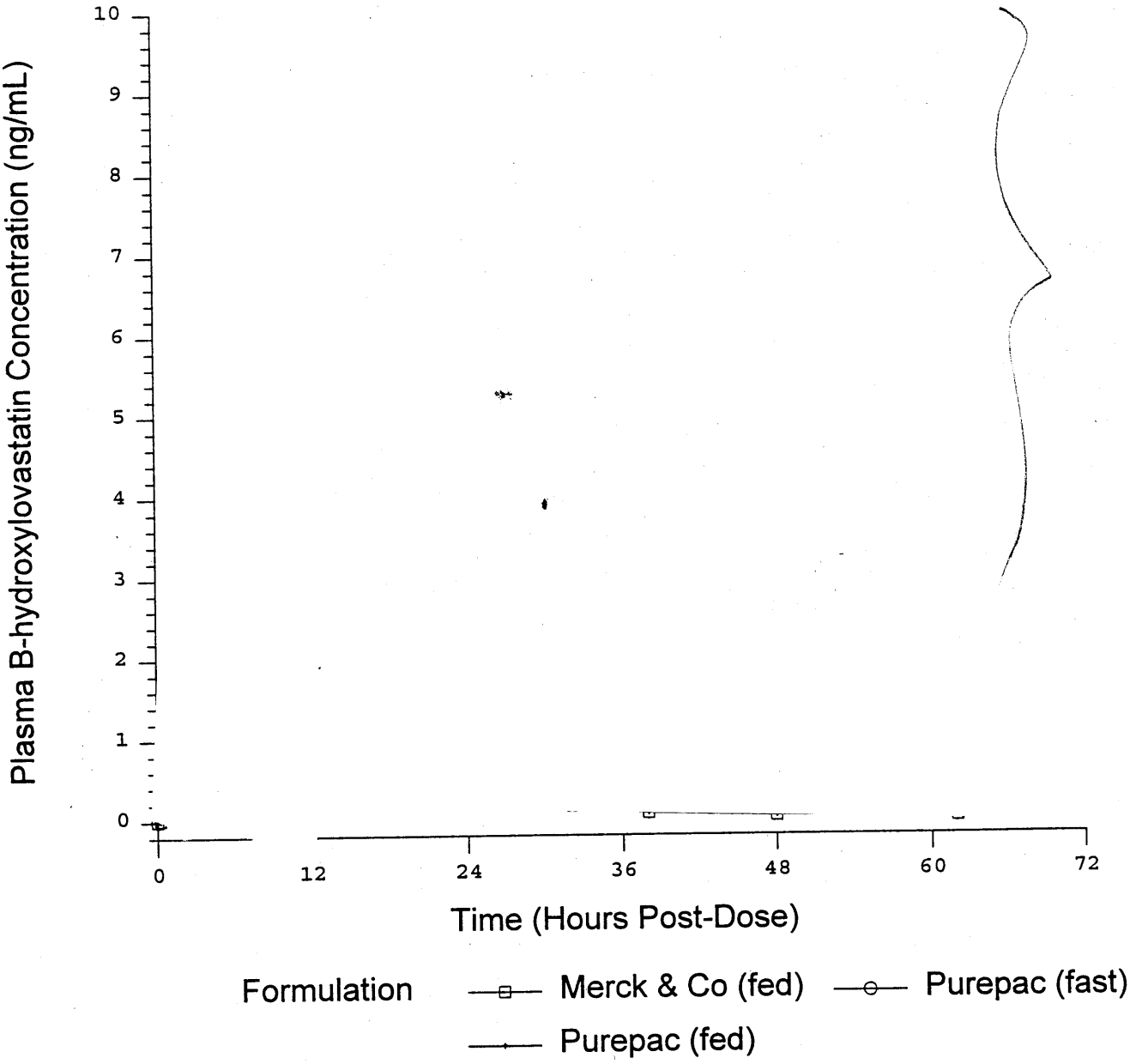


Figure 2. Beta-HYDROXYLOVASTATIN PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME, SINGLE-DOSE FASTING STUDY #992259

(LINEAR PLOT)

Figure 4. Beta-HYDROXYLOVASTATIN PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME, FED/FASTING SINGLE-DOSE STUDY #992517
(LINEAR PLOT)



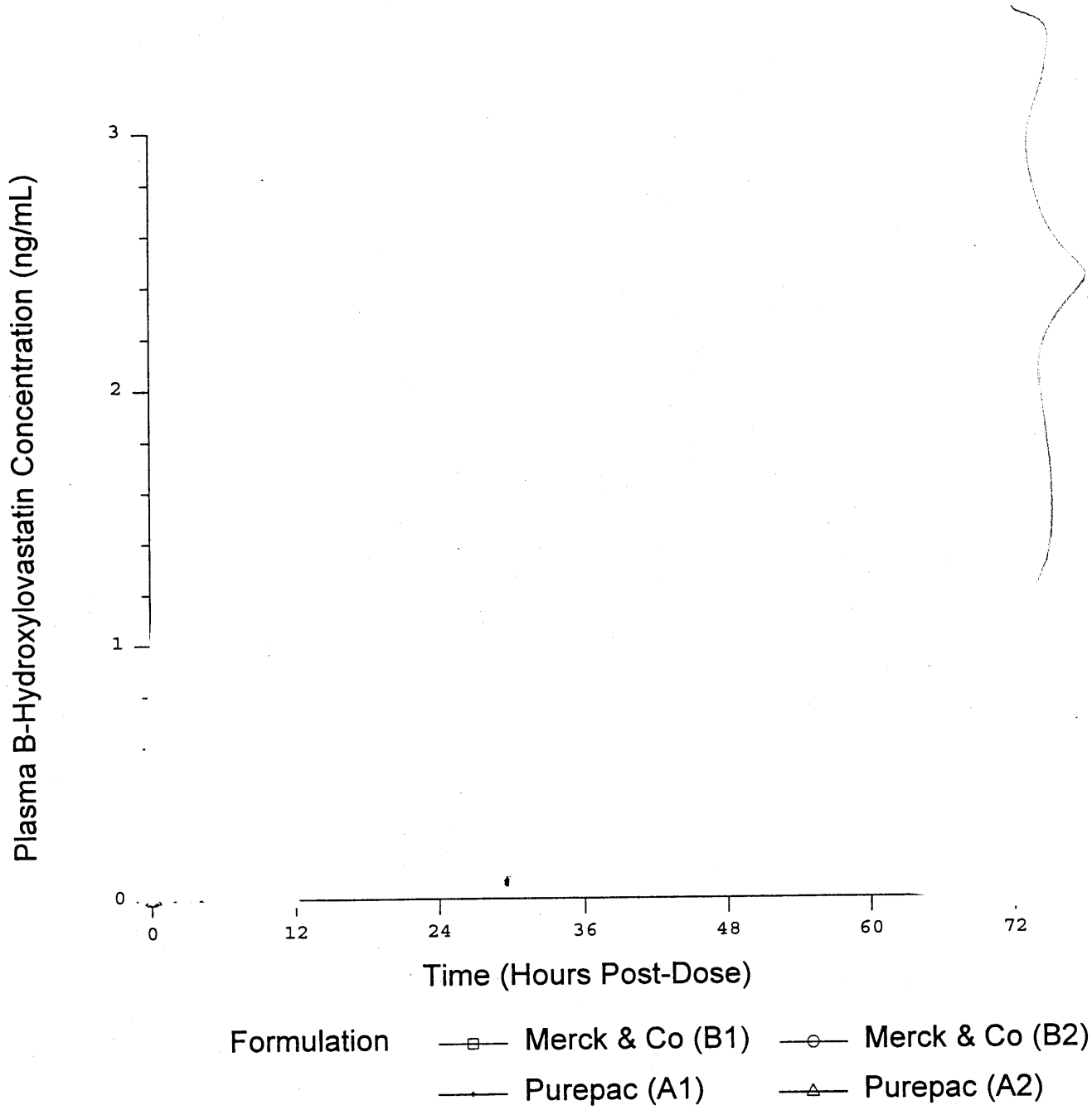


Figure 2. Beta-HYDROXYLOVASTATIN PLASMA CONCENTRATIONS (NG/ML) VERSUS TIME, SINGLE-DOSE FASTING STUDY #992259

(LINEAR PLOT)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-828

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 75-828
FIRM: Purepac Pharmaceutical Company
Attention: Janak Jadeja
200 Elmora Avenue
Elizabeth, NJ 07207
DOSAGE FORM: Tablet
STRENGTH: 10, 20 and 40 mg
DRUG: Lovastatin

CGMP STATEMENT/EIR UPDATED STATUS:
An EER was issued for the indicated firms on 4/19/00. EER was "Withhold" on 4/10/01 as per W. Laborador Ortiz of HFD-320. EER was found acceptable for all listed firms (Purepac and [redacted] on 8/30/01 as per J.D. Ambrogio of HFD-324.

BIOEQUIVALENCY STATUS: Currently Satisfactory. Office level Bioequivalence signoff occurred on 8/21/00, and there were no further questions at that time.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Method validation by the District Laboratory is not required for the approval of the application.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Purepac has provided adequate information on the container/closure components utilized for packaging each of the three strengths of the drug product. Each of the strengths will be packaged into c/c systems as outlined in the table below. Refer to the Table in the Chemistry Review #1 for complete information on the c/c systems utilized by Purepac. Note that the c/c systems utilized for the different strengths use c/c systems of identical configuration containing the same components.

	Strength		
Package Sizes	10 mg	20 mg	40 mg
30's (CRC)	Yes	Yes	Yes
60's (CRC)	Yes	Yes	Yes
90's (CRC)	No	Yes	Yes
100's (CRC)	Yes	Yes	Yes
100's	Yes	Yes	Yes
500's	Yes	Yes	Yes
1000's	Yes	Yes	Yes

LABELING: Satisfactory. Updated FPL submitted for Final Approval is satisfactory as per Labeling Approval Summary dated 6/28/01.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):
Purepac has provided Batch Manufacturing Records for each of the three batches of Lovastatin Tablets manufactured. Purepac has provided the following information on the exhibit batches and proposed production batches:

Lovastatin Tablets			
	Exhibit Batch Size		Commercial Batch Size
Strength	Theoretical	Actual	Theoretical
10 mg	tabs	tabs	tabs
20 mg	tabs	tabs	tabs
40 mg	tabs	tabs	tabs

Purepac has indicated that the proposed commercial production batches reflect the same formulation and method of manufacture as was used to manufacture the exhibit batches to support the ANDA submission. The scale-up and scale-down represented in the above table fall within the recommendations established by OGD.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?): The exhibit batch for the Lovastatin Tablets 40 mg was used in the bioequivalence studies as well as the stability studies.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? The production batch sizes for the Lovastatin tablets USP 10, 20 and 40 mg are as indicated in the table above. The manufacturing and process for the production batches are the same as the exhibit batches.

cc: ANDA #75-828
HFD-600/Reading File
Endorsements:
HFD-625/K.Furnkranz/9/5/
HFD-625/M.Smela, T/L/9/[illegible]/01

9/12/01

9/12/01

V:\firmsnz\purepac\ltrs&rev\75828finalapp.sum2.kjf.doc
F/T by: DJ 9/6/01
Final Approval Summary #2

MODE = MEMORY TRANSMISSION START=SEP-13 14:50 END=SEP-13 14:52

FILE NO.=930

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	8	919086592440	004/004	00:01:08

-FDA CDER OGD CHEMI -

********** - - ***** - - *********

ANDA 75-828

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Purepac Pharmaceutical Co. TEL: (908) 659-2430

ATTN: Joan Janulis FAX: (908) 659-2440

FROM: Michelle Dillahunt PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated March 29, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg.

We are pleased to inform you that this application remains TENTATIVELY APPROVED!

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-828 **Date of Submission: March 29, 2000**
Applicant's Name: Purepac Pharmaceutical Company
Established Name: Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg
Labeling Deficiencies:

1. CONTAINER (10 mg-30's, 60's, 100's, 500's, and 1000's; 20 mg and 40 mg- 30's, 60's, 90's, 100's, 500's, and 1000's)

   a. Satisfactory in draft.

2. INSERT

   a. CLINICAL PHARMACOLOGY (Clinical Studies) – first sentence- Revise " — to read "LDL".

   b. CONTRAINDICATIONS – **BOLD** the penultimate sentence, which reads:
   Lovastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive.

   c. WARNINGS

      i. (Skeletal Muscle) – **BOLD** the second sentence of this subsection, which reads:
      Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time.

      ii. (Reducing the risk of Myopathy)
         A. BOLD the following:
            1. **General Measures. Patients starting therapy with lovastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness, or weakness.**
         B. BOLD the penultimate sentence of paragraph one under "General Measures" which reads:
         Lovastatin therapy should be discontinued if myopathy is diagnosed or suspected.
         C. BOLD the following:
            2. **Measures to reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS, *Drug Interactions*). Physicians contemplating combined therapy with lovastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug.**
         D. Under 2., last paragraph, BOLD the first sentence up to the parenthesis.
      iii. (Liver Dysfunction)
         A. BOLD the first sentence of the first paragraph of this subsection.
         B. BOLD the first sentence of the second paragraph of this subsection

   d. PRECAUTIONS (Carcinogenesis, Mutagenesis, Impairment of Fertility) –
      i. Fifth paragraph, sentence one- Revise to read as follows:
      ...was administered to mice for 72 weeks...
      Note: Change ' — to "for".
      ii. Fifth paragraph, sentence two – Revise to read as follows:
      ...females and mid- and high dose males,...
      Note: Change " [redacted] to "males".

e. ADVERSE REACTIONS (Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Clinical Adverse Experiences) – Second Sentence – Revise "—" to read "≥1%".

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes- http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

/S/

Wm. Peter Rickman,
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-828

CORRESPONDENCE

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

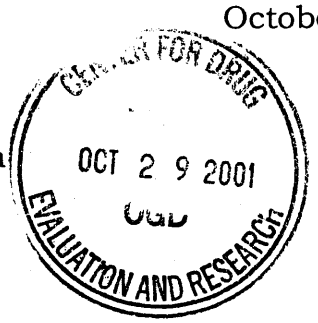
Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

MINOR AMENDMENT
(CMC Information)

ORIG AMENDMENT
N/AM

UPS OVERNIGHT COURIER

October 26, 2001



Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: #75-828, Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg

Dear Mr. Buehler:

Reference is made to our March 29, 2000 submission of an Abbreviated New Drug Application for Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg, ANDA #75-828. Further reference is made to your September 13, 2001 letter stating that this application is tentatively approved. Purepac Pharmaceutical Co. hereby submits this Minor Amendment to the referenced Abbreviated New Drug Application in accordance with the provisions in the tentative approval letter dated September 13, 2001.

Purepac is hereby submitting this Minor Amendment containing updated chemistry, manufacturing and controls (CMC) information. Provided in this amendment is a copy of Purepac's alternate commercial scale master formulae (MF) for the 10 mg and 40 mg strengths. The scale-up batch size meets the requirements OGD Policy and Procedure Guide #22-90 as follows:

1. The test batches supporting this application represent at least [redacted], of the number of finished dosage units proposed for each production-scale batch size.
2. The type of equipment used in the production of test batches is the same as that intended for use in the production of commercial size batches.
3. The formulation for the test batches and the proposed commercial production batches are the same.
4. The alternate commercial batch sizes will be validated prior to implementation.

10/29/01

We are proposing these alternate commercial scale batch sizes in order to meet potential commercial demand. Please refer to Section 1 of this amendment for the following supporting documentation:

- List of changes,
- Equipment comparison tables,
- Copies of the alternate commercial scale master formulae.

In conjunction with this submission, Purepac is providing a copy of this amendment to our local district office. The required Field Copy Certification is included in Section 2 of this submission.

This concludes our **MINOR AMENDMENT** in response to the Agency's request. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/js
Enclosures

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

(CMC Information)

UPS OVERNIGHT COURIER

August 20, 2001

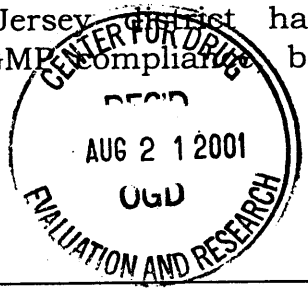
Mr. Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-828, Lovastatin Tablets USP, 10 mg, 20 mg & 40 mg

Dear Mr. Buehler:

Reference is made to our March 29, 2000 submission of an Abbreviated New Drug Application for Lovastatin Tablets USP, 10 mg, 20 mg & 40 mg ANDA #75-828. Further reference is made to your August 15, 2001 letter requesting the submission of a Minor Amendment to the pending application at the time we satisfactorily resolve the cGMP related issues associated with our manufacturing facility.

In accordance with your request, Purepac is providing a statement that representatives of the New Jersey district have determined that our manufacturing facility is in cGMP compliance based on our most recent inspection.



In conjunction with this submission, Purepac is providing a copy of this amendment to our local district office. The required Field Copy Certification is included in this amendment.

This concludes our **MINOR AMENDMENT** in response to your letter of August 15, 2001. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

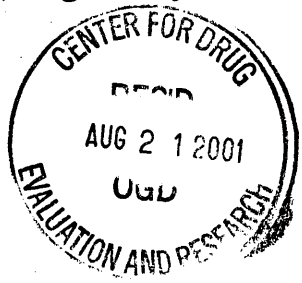
Sincerely,

PUREPAC PHARMACEUTICAL CO.

Elizabeth Troobridge/for

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/bt



ANDA 75-828

AUG 15 2001

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

Dear Madam:

This is in reference to your abbreviated new drug application dated March 29, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg.

Reference is also made to our tentative approval letter dated December 19, 2000 and to your amendment dated June 14, 2001.

We have completed the review of this abbreviated application and have concluded that this application is deficient and, therefore, not approvable under 21 CFR 314.125 (b)(13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging or holding of the drug product comply with current good manufacturing practice (CGMP) regulations.

Our conclusion is based upon the findings revealed during an initial inspection of Purepac by representatives of the United States Food and Drug Administration from January 23, 2001 through March 12, 2001. Upon review of the inspector's report and observations noted during this inspection, we have received a recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, to withhold approval of your abbreviated application.

Until such time as it can be determined to the Agency that the CGMP-related issues associated with Purepac's manufacture of Lovastatin have been corrected and the Agency's concerns are otherwise satisfied, your application cannot be approved. We note that arrangements are currently being made by the Office of Compliance to reinspect the facility.

You should amend this application when the CGMP-related issues have been satisfactorily resolved. Your amendment to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct the deficiencies, then the amendment will be considered to represent a MAJOR AMENDMENT.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 8/14/01

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

ORIG AMENDMENT

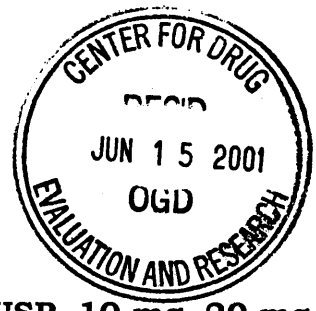
N/AM

MINOR AMENDMENT
(CMC and Labeling Information)

UPS OVERNIGHT COURIER

June 14, 2001

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773



RE: ANDA #75-828, Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg

Dear Mr. Buehler:

Reference is made to our March 29, 2000 submission of an Abbreviated New Drug Application for Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg, ANDA #75-828. Further reference is made to your December 19, 2000 letter stating that this application is tentatively approved, and your June 13, 2001 facsimile requesting labeling changes.

Purepac Pharmaceutical Co. hereby submits this Minor Amendment to the referenced Abbreviated New Drug Application in accordance with the provisions in the tentative approval letter dated December 19, 2000. This amendment provides revised package outsert labeling as per the agency's facsimile dated June 13, 2001, containing the innovator's newly approved labeling for Mevacor® Tablets. In addition to the required revisions, please note that Purepac has revised the insert to be in an outsert format.

Enclosed please find twelve (12) copies of final printed outsert labeling for your review. Also included in this submission is a side-by-side comparison of our proposed outsert and the listed drug's insert with all differences annotated and explained. If this meets with your approval, please consider this as final printed outsert labeling.

/s/ 6-19-01

MINOR AMENDMENT

RE: ANDA #75-828, Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg

Please be advised that since there is no chemistry, manufacturing and controls (CMC) related change brought to this application, there is no updated information available to provide in this amendment.

This concludes our **MINOR AMENDMENT** in response to the Agency's request. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/cah
Enclosures

APPEARS THIS WAY
ON ORIGINAL

PUREPAC PHARMACEUTICAL CO.
FAX NO. (908) 659-2440

TELEFAX / MEMORANDUM

TO: Ms Michelle Dillahunt
Project Manager
OGD, CDER, FDA

ORIG AMENDMENT
N/FA

FAX NO. (301) 827 4337

FROM: Janak Jadeja
Manager, Regulatory Affairs

SUBJECT: ANDA # 75-828, Lovastatin Tablets USP, 10 mg, 20 mg and 40 mg
FAX AMENDMENT

DATE: October 19, 2000

CC: NO. PAGES INCLUDING THIS COVER SHEET: 131

Dear Ms. Dillahunt,

Please find enclosed our response to facsimile deficiency letter from the agency dated September 21, 2000.

Should any question arise, please feel free to contact me.

Sincerely,

Janak Jadeja

**APPEARS THIS WAY
ON ORIGINAL**

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

FACSIMILE AMENDMENT

October 19, 2000

UPS OVERNIGHT COURIER

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC to
Fax with 5
10/11/00

RE: ANDA #75-828
Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg

Dear Mr. Buehler:

Reference is made to our March 29, 2000 submission of an Abbreviated New Drug Application for Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg, ANDA #75-828. Further reference is made to your September 21, 2000 facsimile identifying chemistry, and labeling deficiencies and comments from the Division of Bioequivalence. Your comments are provided in bold type followed by our response.

CENTER FOR EVALUATION AND RESEARCH
RECD
OCT 20
OGD

Chemistry Deficiencies

A. Deficiencies

Agency Comment

1. **Please include the test for Residue on Ignition for the drug substance, as is required in the current USP Monograph for Lovastatin.**

Purepac's Response

The test for Residue on Ignition for the drug substance, as is required in the current USP Monograph for Lovastatin, is included on the raw material specification sheet. Please refer to page 5507 of the original application. A copy of the current specification sheet is also included in Section 1 of this amendment.

/S/ 10/19/00

Redacted 3

pages of

trade secret and/or

confidential

commercial

information

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Agency Comment

1. A satisfactory CGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

Purepac's Response

Purepac acknowledges that a satisfactory CGMP compliance evaluation for the firms referenced in the ANDA is required for approval.

Agency Comment

2. Please submit any additional long-term stability data generated since your last submission.

Purepac's Response

The additional long-term stability data is provided for all three strengths of Lovastatin Tablets USP in Section 5.

Agency Comment

3. Labeling deficiencies must also be addressed in your response.

Purepac's Response

Labeling deficiencies are addressed in the appropriate section below.

BIOEQUIVALENCY COMMENTS

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

Purepac's Response

Purepac acknowledges the comment from the Division of Bioequivalence regarding the above noted dissolution testing specifications. Please be advised that our current finished product and stability specification sheets reflect the referenced dissolution testing.

LABELING DEFICIENCIES:

1. **CONTAINER – (10 mg-30's, 60's, 100's, 500's, and 1000's; 20 mg and 40 mg-30's, 60's, 90's, 100's, 500's, and 1000's)**

   Satisfactory in draft.

2. **INSERT (*specific comments are not included in this letter*)**

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes – http ;//www.fda.gov/cder/org/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94 (a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Purepac's Response

All labeling deficiencies were corrected as requested. To facilitate review, and in accordance with 21 CFR 314.94 (a) (8) (iv), a side-by-side insert comparison with all the differences annotated and explained is provided in Section 6 along with 12 copies of final printed labels and labeling.

In addition, please be advised that the diskettes (in duplicate) containing the Electronic Submission Documents (ESDs) for the chemistry, manufacturing and controls review part of this amendment, as applicable, is included with the hard copy of this amendment. Purepac Pharmaceutical Company declares that the data contained in the Electronic Submission Documents are identical to the information contained in the Archival and Review copies of the amendment with the exceptions/explanations provided in Section 7. Please note that EVA version 4.14 was utilized for completing the ESDs in this amendment and that our originally submitted companion document remains unchanged.

In conjunction with this submission, Purepac is providing a copy of the amendment to our local district office. The required Field Copy Certification is included in Section 8 of this submission.

This concludes our **Facsimile Amendment** in response to your letter dated September 21, 2000. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/js
Enclosures: Two (2) Diskettes in the hard copy
CMC EVA ESDs (Original and Duplicate)

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

BIOEQUIVALENCY AMENDMENT

UPS OVERNIGHT COURIER

June 28, 2000

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/A B

RE: ANDA #75-828, Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg

Dear Mr. Buehler:

Reference is made to our March 29, 2000 submission of an Abbreviated New Drug Application for Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg ANDA #75-828. Further reference is made to your Bioequivalency deficiency letter dated June 5, 2000 (copy enclosed). Your comments are provided in bold type, followed by our response.

Agency Comment

1. **Fasting and non-fasting studies: You are requested to calculate elimination rate constant, $AUC_{0\text{-}inf}$, and elimination half-life of lovastatin as well as beta-hydroxylovastatin. Please include these data with other pharmacokinetic parameters and submit the revised data files.**

Purepac's Response

The pharmacokinetic reports are amended by [redacted] to include calculated elimination rate constant, $AUC_{0\text{-}inf}$, and elimination half-life of lovastatin as well as beta-hydroxylovastatin. The amended pages are identified as Report Amendment No. 2 and are included in Section 2. Refer to pages 4-8 and 285-289 for a detailed summary of changes for the fasting and food effect study, respectively. Please note that the enclosed diskette presents this data in 'Standard FDA' format as well as in 'EVA' format. The files in standard FDA format are provided as an alternative option for the reviewer and are included on diskette in a folder labeled 'Updated Data'.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 29 2000
OGD

The EVA amendment to our Electronic Submission Documents (ESDs) for the bioavailability/ bioequivalence (BA/BE) section is identified as 'PUR0005' and is included on diskette in the folder labeled 'EVA-Amended'. Purepac Pharmaceutical Company declares that the data contained in the Electronic Submission Document Files is identical to the information contained in this Bioequivalency Amendment. Please note that the information was entered via the most current EVA version, 4.14

Agency Comment

2. Fasting and non-fasting studies: Please submit linear plots of individual subject plasma profiles for lovastatin and beta-hydroxylovastatin.

Purepac's Response

The pharmacokinetic reports are amended by ——— to include the linear plots of individual subject plasma profiles for both analytes. The amended pages are identified as Report Amendment No. 2 and are included in Section 2. Refer to pages 4-8 and 285-289 for a detailed summary of changes for the fasting and food effect study, respectively.

Please note that Report Amendment No. 1 contained a revised Table of Contents to include the Clinical Report as an Appendix. This is superseded by Report Amendment No 2.

This concludes our **BIOEQUIVALENCY AMENDMENT** in response to your letter of June 5, 2000. Purepac Pharmaceutical Co. trusts that you will find this amendment complete and in order, and looks forward to the approval of our Abbreviated New Drug Application. If you have any questions regarding this submission, please do not hesitate to call the undersigned at (908) 659-2430.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ:js
Enclosures

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

75828

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

NC
195

ELECTRONIC SUBMISSION ESD

April 17, 2000

UPS OVERNIGHT COURIER

Mr. Gary J. Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg

Dear Mr. Buehler,

Reference is made to our March 29, 2000 submission of an Abbreviated New Drug Application, for Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg.

In accordance with the Grace Period Announcement that became effective on April 1, 1999, Purepac is hereby submitting the Bioavailability/Bioequivalence and Chemistry, Manufacturing and Controls electronic submission documents (ESDs). The ESDs for both the CMC and BA/BE sections were prepared with the current version of EVA 4.14. The diskettes, submitted in duplicate, contain the information/data files for the BA/BE or CMC review part, as applicable. Therefore, a total of 4 diskettes (1 original and 1 duplicate disk for each review part) are enclosed. Purepac is submitting these electronic Submission Documents within the 30 day grace period permitted from the agency's receipt of our submission.

Purepac Pharmaceutical Company declares that the data contained in the Electronic Submission Document Files is identical to the information contained in the Archival and Review Copies of this application with the following exceptions/explanations:

General:

- The electronic submission date is March 29, 2000, which is the same date as that of submission of the original paper copy.

CMC Section:

- CMC Packaging System for submission: Since the only difference between the development packaging specification and the final packaging specifications is the deletion of the heading "Development Use Only", the ID numbers of the final packaging specifications are referenced in the electronic submission. Please note that the development packaging specifications were utilized for the exhibit batches and were finalized upon completion of accelerated stability studies.

BA/BE Section:

- In preparation of the BE portion of this electronic submission, it was not considered entirely appropriate to present the stability and recovery data in data files with the following extensions: .jaa, .jab, .kac, .kad, .kae and .kaf. These data have been presented in Appendix C of the Companion Document (PUR0001.002).
- Due to the nature of the plasma-concentration data, it was not possible to estimate an elimination rate constant that would be meaningful. Therefore, the associated pharmacokinetic parameters (AUCinf and Half-life) were not reported and no data appears in data files with the following extensions: .naa, .nab, .nac and .nad.
- Due to conflicts with some software applications, the following extensions were skipped: .mad, .maf, .mam and .pab.
- The BA/BE Tables program (released 7/14/98) was ran to determine whether all data files were in the appropriate format; however, the program did not produce a complete listing of all files. Errors were indicated on the some of the files above, where no data were entered. An error was indicated for the .hab file; however, no problems could be detected on extensive review of this file. This was discussed with Richard Sponaugle on April 12-14, 2000, and he indicated that the BE Tables program was not robust. Mr. Sponaugle indicated that these minor deviations might be acceptable, provided that all elements are included in the Companion Document. Note that the number of analytes was specified as four, due to the two different assays used for the two studies. For all practical purposes, there are really two analytes for each study, and samples from each study were separately evaluated by two, individually validated assays. Mr Sponaugle anticipated being able to load the data into the FDA system.
- Please refer to Appendix B of the Companion Document for additional details.

Purepac Pharmaceutical Co. trusts that you will find this application complete and well organized, and looks forward to the review process. If you have any questions concerning this submission, please do not hesitate to contact the undersigned at telephone number (908) 659-2430, or fax number (908) 659-2440.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/js
Four (4) 3 ½" diskettes enclosed

ANDA 75-828

Purepac Pharmaceutical Co.
Attention: Joan Janulis
200 Elmora Avenue
Elizabeth, NJ 07207

APR 19 2000

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated April 12, 2000 and your correspondence dated April 12, 2000.

NAME OF DRUG: Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg

DATE OF APPLICATION: March 29, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 30, 2000

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

A Trusted Name For Over Half A Century

PUREPAC

ORIGINAL

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

NEW CORRESP
NC

April 12, 2000

75-828

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CORRESPONDENCE TO ANDA FILE

RE: Abbreviated New Drug Application for Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg

Dear Mr. Buehler,

Reference is made to the April 12, 2000 telephone conversations between Emily Thomas of OGD Regulatory Support Branch and Joan Janulis and Janak Jadeja of Purepac Pharmaceutical Co., regarding the above referenced ANDA, submitted on March 29, 2000. During this conversation, Ms. Thomas requested that Purepac provide another FDA Form 3454 "Certification: Financial Interests and Arrangements of Clinical Investigators" since the one provided in the original filing did not have any boxes checked. Three new original copies are enclosed bearing signature, today's date, and a mark in box 1, and will replace the existing page 127 in the ANDA.

Purepac Pharmaceutical Co. trusts that you will find the information submitted in this correspondence complete and in order, and looks forward to the review process. If you have any questions concerning this submission, please do not hesitate to contact the undersigned at telephone number (908) 659-2430, or fax number (908) 659-2440.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
APR 13 2000
OGD

JJ/js
Enclosures

A Trusted Name For Over Half A Century

PUREPAC

Purepac Pharmaceutical Co.
200 Elmora Avenue, Elizabeth, New Jersey 07207
908-527-9100
Fax: 908-527-0649

March 29, 2000

Mr. Gary Buehler, Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Abbreviated New Drug Application for Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg

Dear Mr. Buehler,

In accordance with the regulations promulgated under Section 505(j) of the Federal Food, Drug and Cosmetic Act as amended, Purepac Pharmaceutical Co. is submitting this Abbreviated New Drug Application (Archival and Review Copies) for Lovastatin Tablets USP, 10 mg, 20 mg, and 40 mg.

This Abbreviated New Drug Application has been prepared in accordance with the current version of the Guidance for Industry entitled "Organization of an ANDA", dated February 1999, and contains a total of 28 (twenty-eight) volumes, comprising the Archival Copy and the Review Copy (chemistry, manufacturing and controls review part and bioavailability/ bioequivalence review part).

In addition, Electronic Submission Documents (ESDs) for the bioavailability/ bioequivalence (BA/BE) and chemistry, manufacturing and controls (CMC) review parts of this application will be submitted as a correspondence to the ANDA file. The ESDs will be submitted within the 30 day period currently allowed by the Office of Generic Drugs. The required Electronic Submission Document Declaration, stating that the electronic data is identical to the information contained in the Archival and Review copies of the application, will be included with the ESD submission. Please note that the information will be entered via the most current available EVA version, 4.14.

Since Lovastatin Tablets are listed in the USP, Purepac acknowledges the fact that compendial test methods are official for regulatory purposes and will prevail in the case of a dispute.

In conjunction with this submission, Purepac has provided a Field Copy of this application to our local district office in accordance with 21 CFR 314.94(d)(5). Please note that the required Field Copy Certification is contained in **Section XXI** of our abbreviated application. In addition, The following certifications are provided in this submission:

- A certification in accordance with Section 306(K) of the Federal Food Drug and Cosmetic Act as amended by the "Generic Drug Enforcement Act" **(Section XX)**
- A certification regarding the financial interests and arrangements of the clinical investigators responsible for the treatment or evaluation of research subjects enrolled in the bioequivalence studies supporting this application **(Section VI)**

Three (3) separately bound copies of the analytical methods and related descriptive information are also provided with this original ANDA.

Additionally, Purepac acknowledges that all firms referenced in this ANDA, with respect to the manufacture and testing of the subject drug products, must be in compliance with current good manufacturing practices at the time of approval. A signed acknowledgment is contained in **Section IX** of this application. Purepac also acknowledges that all DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA.

Purepac Pharmaceutical Co. trusts that you will find this application complete and well organized, and looks forward to the review process. If you have any questions concerning this submission, please do not hesitate to contact the undersigned at telephone number (908) 659-2430, or fax number (908) 659-2440.

Sincerely,

PUREPAC PHARMACEUTICAL CO.

Joan Janulis, R.A.C.
Vice President, Regulatory Affairs

JJ/js
Enclosures