CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020740/S03

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-740/S-003

JAN 4 1999

Bayer Corporation Pharmaceutical Division
Attention: Nancy C. Motola, Ph.D.
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516

Dear Dr. Motola:

Please refer to your supplemental new drug application dated July 21, 1998, received July 22, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Baycol (cerivastatin sodium tablets).

We acknowledge receipt of your submissions dated July 27, August 31, and September 28, 1998.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides labeling changes in draft form to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the Baycol package insert. These changes include:

CLINICAL PHARMACOLOGY

In the Pharmacokinetics: Metabolism sections "benzylic methyl ether" was changed to "pyridilic methyl ether".

INDICATIONS AND USAGE

In Table 2-NCEP Treatment Guidelines:
The last entry in the "Goal" column was corrected to "$\leq$ 100 ($\leq$2.6)".

WARNINGS

Under the Skeletal Muscle subsection, the wording of the first sentence has been changed to "Rare cases of rhabdomyolysis (some with acute renal failure secondary to myoglobinuria) have been reported with cerivastatin and other drugs in this class." The wording was changed

from "Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with other HMG CoA reductase inhibitors."

PRECAUTIONS

The section titled "Other Concomitant Therapy" under the DRUG INTERACTIONS subsection has been deleted.

ADVERSE REACTIONS

Addition of the following section:
"Post-Marketing Adverse Event Reports: The following events have been reported since market introduction. While these events were temporally associated with the use of Baycol, a causal relationship to the use of Baycol cannot be readily determined due to the spontaneous nature of reporting of medical events, and the lack of controls: hepatitis, myositis, rhabdomyolysis, some with associated renal failure (most cases involved concomitant gemfibrozil), urticaria, angioedemia, visual disturbance, blurred vision."

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

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted September 28, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-740/S-003." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

If you have any questions, contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely,

/S/ 1/4/99

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020740/S03

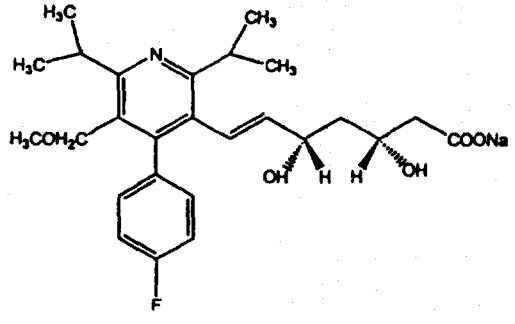
FINAL PRINTED LABELING

BAYCOL®

(cerivastatin sodium tablets)

DESCRIPTION

Cerivastatin sodium is sodium [S-[R*,S*-(E)]]-7-[4-(4-fluorophenyl)-5-methoxymethyl)-2,6bis(1-methylethyl)-3-pyridinyl]-3,5-dihydroxy-6-heptenoate. The empirical formula for cerivastatin sodium is $C_{26}H_{33}FNO_5Na$ and its molecular weight is 481.5. It has the following chemical structure:



Cerivastatin sodium is a white to off-white hygroscopic amorphous powder that is soluble in water, methanol, and ethanol, and very slightly soluble in acetone. Cerivastatin sodium is an entirely synthetic, enantiomerically pure inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

BAYCOL® (cerivastatin sodium tablets) is supplied as tablets containing 0.2 or 0.3 mg of cerivastatin sodium, for oral administration. Active Ingredient: cerivastatin sodium. Inactive Ingredients: mannitol, magnesium stearate, sodium hydroxide, crospovidone, povidone, iron oxide yellow, methylhydroxypropylcellulose, polyethylene glycol, and titanium dioxide.

CLINICAL PHARMACOLOGY

Cholesterol and triglycerides circulate as part of lipoprotein complexes throughout the bloodstream. These complexes can be separated via ultracentrifugation into high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) fractions. In the liver, cholesterol and triglycerides (TG) are synthesized, incorporated into VLDL, and released into the plasma for delivery to peripheral tissues.

A variety of clinical studies have demonstrated that elevated levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (apo-B, a membrane complex for LDL-C) promote human atherosclerosis. Similarly, decreased levels of HDL-C (and its transport complex, apolipoprotein A) are associated with the development of atherosclerosis. Epidemiologic investigations have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C.

In patients with hypercholesterolemia, BAYCOL® (cerivastatin sodium tablets) has been shown to reduce plasma total cholesterol, LDL-C, and apolipoprotein B. In addition, it also reduces plasma triglycerides and increases plasma HDL-C. The agent has no consistent effect on plasma Lp(a). The effect of BAYCOL® on cardiovascular morbidity and mortality has not been determined.

Mechanism of Action: Cerivastatin is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis by cerivastatin reduces the level of cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors, thereby increasing the uptake of cellular LDL particles. The end result of these biochemical processes is a reduction of the plasma cholesterol concentration.

Pharmacokinetics:

Absorption:

BAYCOL® (cerivastatin sodium tablets) is administered orally in the active form. The mean absolute bioavailability of cerivastatin following a 0.2-mg tablet oral dose is 60% (range 39 - 101%). In general, the coefficient of variation (based on the inter-subject variability) for both systemic exposure (area under the curve, AUC) and C_{max} is in the 20% to 40% range. The bioavailability of cerivastatin sodium tablets is equivalent to that of a solution of cerivastatin sodium. No unchanged cerivastatin is excreted in feces. Cerivastatin exhibits linear kinetics over the dose range of 0.05 to 0.3 mg daily. Mean maximum concentrations (C_{max}) following evening cerivastatin tablet doses of 0.05, 0.1, 0.2, and 0.3 mg are 0.6, 1.3, 2.4, and 3.8 µg/L, respectively. AUC values are also dose–proportional over this dose range and the mean time to maximum concentration (t_{ax}) is approximately 2.5 hours for all dose strengths. Following oral administration, the terminal elimination half-life ($t_{1/2}$) for cerivastatin is 2 to 3 hours. Steady-state plasma concentrations show no evidence of cerivastatin accumulation following administration of up to 0.4 mg daily.

Results from an overnight pharmacokinetic evaluation following single-dose administration of cerivastatin with the evening meal or 4 hours after the evening meal showed that administration of cerivastatin with the evening meal did not significantly alter either AUC or C_{max} compared to dosing the drug 4 hours after the evening meal. In patients given 0.2 mg cerivastatin sodium once daily for 4 weeks, either at mealtime or at bedtime, there were no differences in the lipid-lowering effects of cerivastatin. Both regimens of 0.2 mg once daily were slightly more efficacious than 0.1 mg twice daily.

Distribution: The volume of distribution (VD_{ss}) is calculated to be 0.3 L/kg. More than 99% of the circulating drug is bound to plasma proteins (80% to albumin). Binding is reversible and independent of drug concentration up to 100 mg/L.

Metabolism: Biotransformation pathways for cerivastatin in humans include the following: demethylation of the pyridilic methyl ether to form M1 and hydroxylation of the methyl group in the 6'-isopropyl moiety to form M23. The combination of both reactions leads to formation of metabolite M24. The major circulating blood components are cerivastatin and the pharmacologically active M1 and M23 metabolites. The relative potencies of metabolites M1 and M23 are approximately 50% and 80% of the parent compound, respectively. Following a 0.3-mg dose of cerivastatin to 6 healthy volunteers, mean C_{max} values for cerivastatin, M1, and M23 were 3.0, 0.2, and 0.5 µg/L, respectively. Therefore, the cholesterol-lowering effect is due primarily to the parent compound, cerivastatin.

Excretion: Cerivastatin itself is not found in either urine or feces; M1 and M23 are the major metabolites excreted by these routes. Following an oral dose of 0.4 mg ^{14}C-cerivastatin to healthy volunteers, excretion of radioactivity is about 24% in the urine and 70% in the feces. The parent compound, cerivastatin, accounts for less than 2% of the total radioactivity excreted. The plasma clearance for cerivastatin in humans after intravenous dosing is 12 to 13 liters per hour.

SPECIAL POPULATIONS

Geriatric:	Plasma concentrations of cerivastatin are similar in healthy elderly male subjects (>65 years) and in young males (<40 years).
Gender:	Plasma concentrations of cerivastatin in females are slightly higher than in males (approximately 12% higher for C_{max} and 16% higher for AUC)
Pediatric:	Cerivastatin pharmacokinetics have not been studied in pediatric patients.

Race: Cerivastatin pharmacokinetics were compared across studies in Caucasian, Japanese and Black subjects. No significant differences in AUC, C_{max}, t_{max}, and $t_{1/2}$ were found.

Renal: Steady-state plasma concentrations of cerivastatin are similar in healthy volunteers (Cl_{Cr}>90 mL/min/1.73m^2) and in patients with mild renal impairment (Cl_{Cr} 61-90 mL/min/1.73m^2). In patients with moderate (Cl_{Cr} 31-60 mL/min/1.73m^2) or severe (Cl_{Cr} ≤30 mL/min/1.73m^2) renal impairment, AUC is up to 60% higher, C_{max} up to 23% higher, and $t_{1/2}$ up to 47% longer compared to subjects with normal renal function.

Hemodialysis: While studies have not been conducted in patients with end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of cerivastatin since the drug is extensively bound to plasma proteins.

Hepatic: Cerivastatin has not been studied in patients with active liver disease (see CONTRAINDICATIONS). Caution should be exercised when BAYCOL® (cerivastatin sodium tablets) is administered to patients with a history of liver disease or heavy alcohol ingestion (see WARNINGS).

Clinical Studies: BAYCOL® (cerivastatin sodium tablets) has been studied in controlled trials in North America, Europe, Israel, and South Africa and has been shown to be effective in reducing plasma total cholesterol (Total-C) and LDL cholesterol (LDL-C) in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia. Over 2,800 patients with Type IIa and IIb hypercholesterolemia were treated in trials of 4 to 104 weeks duration. In a 24-week, randomized, double-blind, placebo-controlled US trial in 934 patients with primary hypercholesterolemia, BAYCOL® (cerivastatin sodium tablets) 0.05 to 0.3 mg once daily produced dose-related reductions in plasma LDL-C and Total-C. Significant reductions in mean total-C and LDL-C were evident after one week, peaked at four weeks, and were maintained for the duration of the trial. Reductions in plasma triglycerides (TG) and increases in HDL-C were also observed. The results from this study in patients treated with the marketed doses of cerivastatin are summarized in Table 1.

Table 1
Response in Patients with Primary Hypercholesterolemia
Mean Percent Change from Baseline after 24 Weeks

Dosage	n	Total-C	LDL-C	HDL-C	TG	Apo-B
Placebo	137*	+1.7	+1.8	+3.1	+1.1	+3.2
BAYCOL®						
0.2 mg qd**	143†	-17.4	-25.3	+10.4	-10.7	-18.7
0.3 mg qd**	135‡	-19.4	-28.2	+10.3	-12.7	-20.5

* 137 patients were evaluated for all parameters except LDL-C which had 136 patients

† 143 patients were evaluated for Total-C, HDL-C and TG. For LDL-C and Apo-B there were 140 and 141 patients evaluated, respectively.

‡ 135 patients were evaluated for all parameters except LDL-C which had 134 patients.

** qd = once daily

In a separate dose-scheduling study, BAYCOL® (cerivastatin sodium tablets) was given as either a 0.2-mg dose once daily with dinner or at bedtime or as a 0.1-mg dose twice daily (morning and evening). Mean LDL-C reduction in response to BAYCOL® dosed once with dinner or at bedtime was about 4% greater than the mean reduction in response to twice daily (divided) dosing ($p<0.05$).

INDICATIONS AND USAGE

Therapy with lipid-altering drugs should be a component of multiple risk factor intervention in those patients at significantly high risk for atherosclerotic vascular disease due to hypercholesterolemia. BAYCOL® (cerivastatin sodium tablets) is indicated as an adjunct to diet for the reduction of elevated total and LDL cholesterol levels in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb) when the response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures alone has been inadequate.

Before considering therapy with lipid-altering agents, secondary causes of 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 triglycerides (TG). For patients with TG less than 400 mg/dL, LDL-C can be estimated using the following equation:

LDL-C = [Total-C] minus [HDL-C + TG/5]

For TG levels > 400 mg/dL, this equation is less accurate and LDL-C concentrations should be directly measured by preparative ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated Total-C. In such cases, BAYCOL® (cerivastatin sodium tablets) is not indicated.

Lipid determinations should be performed at intervals of no less than four weeks.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized in Table 2.

Table 2

National Cholesterol Education Program (NCEP) Treatment Guidelines

LDL-Cholesterol mg/dL (mmol/L)

Definite Atherosclerotic Disease*	Two or More Other Risk Factors**	Initiation Level***	Goal
NO	NO	≥ 190 (≥ 4.9)	< 160 (<4.1)
NO	YES	≥ 160 (≥ 4.1)	< 130 (<3.4)
YES	YES or NO	≥ 130 (≥ 3.4)	≤ 100 (≤2.6)

* Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

** Other risk factors for coronary heart disease (CHD) include the following: age (males: ≤ 45 years; females: ≤55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C < 35 mg/dL (< 0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≤60 mg/dL (≤1.6 mmol/L).

*** In CHD patients with LDL-C levels 100-129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.

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

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 BAYCOL® may be useful to reduce elevated LDL-cholesterol 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).[1]

CONTRAINDICATIONS

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. Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Cerivastatin sodium should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this drug, cerivastatin sodium should be discontinued and the patient should be apprised of the potential hazard to the fetus.

Hypersensitivity to any component of this medication.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors have been associated with biochemical abnormalities of liver function. Persistent increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal (occurring on two or more not necessarily sequential occasions) have been reported in less than 1.0% of patients treated with cerivastatin sodium in the US over an average period of 11 months. Most of these abnormalities occurred within the first 6 weeks of treatment, resolved after discontinuation of the drug, and were not associated with cholestasis. In most cases, these biochemical abnormalities were asymptomatic.

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) return to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of cerivastatin sodium therapy is recommended.

Active liver disease or unexplained transaminase elevations are contraindications to the use of BAYCOL® (cerivastatin sodium tablets) (see **CONTRAINDICATIONS**). Caution should be exercised when cerivastatin sodium is administered to patients with a history of liver disease or heavy alcohol ingestion (see **CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism**). Such patients should be started at the low end of the recommended dosing range and closely monitored.

Skeletal Muscle: **Rare cases of rhabdomyolysis (some with acute renal failure secondary to myoglobinuria) have been reported with cerivastatin and other drugs in this class.** Myopathy, defined as muscle aching or muscle weakness, associated with increases in plasma creatine kinase (CK) values to greater than 10 times the upper limit of normal, was rare (<0.2%) in U.S. cerivastatin clinical trials. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CK. Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. BAYCOL® (cerivastatin sodium tablets) therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. **BAYCOL® (cerivastatin sodium tablets) should be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with HMG-CoA reductase inhibitors is increased with

concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, azole antifungals or lipid-lowering doses of niacin.

Uncomplicated myalgia has been observed infrequently in patients treated with cerivastatin sodium at rates that could not be distinguished from placebo.

The use of fibrates alone occasionally may be associated with myopathy. The combined use of HMG-CoA inhibitors and fibrates generally should be avoided.

PRECAUTIONS

General: Before instituting therapy with BAYCOL® (cerivastatin sodium tablets), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND USAGE).

Cerivastatin sodium may elevate creatine kinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with cerivastatin sodium.

Homozygous Familial Hypercholesterolemia: Cerivastatin sodium has not been evaluated in patients with rare homozygous familial hypercholesterolemia. HMG-CoA reductase inhibitors have been reported to be less effective in these patients because they lack functional LDL receptors.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

DRUG INTERACTIONS:

Immunosuppressive Drugs, Fibric Acid Derivatives, Niacin (Nicotinic Acid), Erythromycin, Azole Antifungals: See WARNINGS: Skeletal Muscle.

ANTACID (Magnesium-Aluminum Hydroxide): Cerivastatin plasma concentrations were not affected by co-administration of antacid.

CIMETIDINE: Cerivastatin plasma concentrations were not affected by co-administration of cimetidine.

CHOLESTYRAMINE: The influence of the bile-acid-sequestering agent cholestyramine on the pharmacokinetics of cerivastatin sodium was evaluated in 12 healthy males in 2 separate randomized crossover studies. In the first study, concomitant administration of 0.2 mg cerivastatin sodium and 12 g cholestyramine resulted in decreases of more than 22% for AUC and 40% for C^{max} when compared to dosing cerivastatin sodium alone. However, in the second study, administration of 12 g cholestyramine 1 hour before the evening meal and 0.3 mg cerivastatin sodium approximately 4 hours after the same evening meal resulted in a decrease in the cerivastatin AUC of less than 8%, and a decrease in C_{max} of about 30% when compared to dosing cerivastatin sodium alone. Therefore, it would be expected that a dosing schedule of cerivastatin sodium given at bedtime and cholestyramine given before the evening meal would not result in a significant decrease in the clinical effect of cerivastatin sodium.

DIGOXIN: Plasma digoxin levels and digoxin clearance at steady-state were not affected by co-administration of 0.2 mg cerivastatin sodium. Cerivastatin plasma concentrations were also not affected by co-administration of digoxin.

WARFARIN: Co-administration of warfarin and cerivastatin to healthy volunteers did not result in any changes in prothrombin time or clotting factor VII when compared to co-administration of warfarin and placebo. The AUC and C_{max} of both the (R) and (S) isomers of warfarin were unaffected by concurrent dosing of 0.3 mg cerivastatin sodium. Co-administration of warfarin and cerivastatin did not alter the pharmacokinetics of cerivastatin sodium.

ERYTHROMYCIN: In hypercholesterolemic patients, steady-state cerivastatin AUC and C_{max} increased approximately 50% and 24% respectively after 10 days with co-administration of erythromycin, a known inhibitor of cytochrome P450 3A4.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production.

Clinical studies have shown that cerivastatin sodium has no adverse effect on sperm production and does not reduce basal plasma cortisol concentration, impair adrenal reserve or have an adverse effect on thyroid metabolism as assessed by TSH. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effect on basal and reserve steroid levels. 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 cerivastatin sodium who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs that may decrease the levels or activity of endogenous steroid hormones, e.g., ketoconazole, spironolactone, or cimetidine.

CNS and other Toxicities: Chronic administration of cerivastatin to rodent and non-rodent species demonstrated the principal toxicologic targets and effects observed with other HMG-CoA reductase inhibitors: Hemorrhage and edema in multiple organs and tissues including CNS (dogs); cataracts (dogs); degeneration of muscle fibers (dogs, rats, and mice); hyperkeratosis in the non glandular stomach (rats and mice, this organ has no human equivalent); liver lesions (dogs, rats, and mice).

CNS lesions were characterized by multifocal bleeding with fibrinoid degeneration of vessel walls in the plexus chorioideus of the brain stem and in the ciliary body of the eye at 0.1 mg/kg/day in the dog. This dose resulted in plasma levels of cerivastatin (C_{max}), that were about 23 times higher than the mean values in humans taking 0.3 mg/day. No CNS lesions were observed after chronic treatment with cerivastatin for up to two years in the mouse (C_{max} up to 7 times that of humans at 0.3 mg/day) and rat (C_{max} up to 2 times that of humans).

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 2-year study was conducted in rats at average daily doses of cerivastatin of 0.007, 0.034, or 0.158 mg/kg. The high dosage level corresponded to plasma drug levels (AUC) of approximately 1 - 2 times the mean human plasma drug concentrations after a 0.3-mg oral dose. Tumor incidences of treated rats were comparable to controls in all treatment groups. In a 2-year carcinogenicity study in mice with average daily doses of cerivastatin of 0.4, 1.8, 9.1, or 55 mg/kg hepatocellular adenomas were significantly increased in male and female mice at ≥9.1 mg/kg and hepatocellular carcinomas were significantly increased in male mice at ≥1.8 mg/kg. These doses were in the range of human exposure (dose of 0.3 mg/day).

No evidence of genotoxicity was observed *in vitro* with or without metabolic activation in the following assays: microbial mutagen tests using mutant strains of *S. typhimurium* or *E. coli*, Chinese Hamster Ovary Forward Mutation Assay, Unscheduled DNA Synthesis in rat primary hepatocytes, chromosome aberrations in Chinese Hamster Ovary cells, and spindle inhibition in human lymphocytes. In addition, there was no evidence of genotoxicity *in vivo* in a mouse Micronucleus Test; there was equivocal evidence of mutagenicity in a mouse Dominant Lethal Test.

In a combined male and female rat fertility study, cerivastatin had no adverse effects on fertility or reproductive performance at doses up to 0.1 mg/kg/day, a dose that produced plasma drug levels (C_{max}) about 1 - 2 times higher than mean plasma drug levels for humans receiving 0.3 mg cerivastatin/day. At a dose of 0.3 mg/kg/day (plasma C_{max} 4 - 5 times the human level), the length of gestation was marginally prolonged, stillbirths were increased, and the survival rate up to day 4 postpartum was decreased. In the fetuses (F1), a marginal reduction in fetal weight and delay in bone development was observed. In the mating of the F1 generation, there was a reduced number of female rats that littered.

In the testicles of dogs treated chronically with cerivastatin at a dose of 0.008 mg/kg/day (approximately 2 fold the human exposure at doses of 0.3 mg based on C_{max}), atrophy, vacuolization of the germinal epithelium, spermatidic giant cells, and focal oligospermia were observed. In another 1-year study in dogs treated with 0.1 mg/kg/day (approximately 23 fold the human exposure at doses of 0.3 mg based on C_{max}), ejaculate volume was small and libido was decreased. Semen analysis revealed an increased number of morphologically altered spermatozoa indicating disturbances of epididymal sperm maturation that was reversible when drug administration was discontinued.

Pregnancy: Pregnancy Category X: (See CONTRAINDICATIONS): Cerivastatin caused a significant increase in incomplete ossification of the lumbar center of the vertebrae in rats at an oral dose of 0.72 mg/kg. Cerivastatin did not cause any anomalies or malformations in rabbits at oral doses up to 0.75 mg/kg. These doses resulted in plasma levels (C_{max}) 6-7 times the human exposure for rats and 3-4 times the human exposure for rabbits (human dose 0.3 mg). Cerivastatin crossed the placenta and was found in fetal liver, gastrointestinal tract, and kidneys when pregnant rats were given a single oral dose of 2 mg/kg.

Safety in pregnant women has not been established. Cerivastatin 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. Rare reports of congenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors. In a review of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or lovastatin, 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 three- to four-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 BAYCOL® during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. If a women becomes pregnant while taking cerivastatin, the drug should be discontinued and the patient advised again as to potential hazards to the fetus.

Nursing Mothers: Based on preclinical data, cerivastatin is present in breast milk in a 1.3:1 ratio (milk:plasma). Because of the potential for serious adverse reactions in nursing infants, nursing women should not take cerivastatin (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: In clinical pharmacology studies, there were no clinically relevant effects of age on the pharmacokinetics of cerivastatin sodium.

Renal Insufficiency: Patients with significant renal impairment ($Cl_{cr} \leq 60$ mL/min/1.73m^2) have increased AUC (up to 60%) and C_{max} (up to 23%) and should be administered BAYCOL® with caution.

Hepatic Insufficiency: Safety and effectiveness in hepatically impaired patients have not been established. Cerivastatin should be used with caution in patients who have a history of liver disease and/or consume substantial quantities of alcohol (see Contraindications and Warnings).

ADVERSE REACTIONS

In the U.S. placebo-controlled clinical studies, discontinuations due to adverse events occurred in 3% of cerivastatin sodium treated patients and in 3% of patients treated with placebo. Adverse reactions have usually been mild and transient. Cerivastatin sodium has been evaluated for adverse events in more than 3,000 patients and is generally well-tolerated.

Clinical Adverse Experiences: Adverse experiences occurring with a frequency ≥2% for marketed doses of cerivastatin sodium, regardless of causality assessment, in U.S. placebo-controlled clinical studies, are shown in the Table 3 below:

Table 3
Adverse Experiences Occurring in ≥2% of Patients in U.S. Placebo-Controlled Clinical Studies

Adverse Event	BAYCOL® (n = 552)	Placebo (n = 247)
Body as a Whole		
Headache	11.8%	12.6%
Accidental Injury	7.1%	6.9%
Flu Syndrome	6.3%	8.1%
Back Pain	4.0%	6.1%
Abdominal Pain	3.4%	3.6%
Asthenia	3.4%	2.8%
Chest Pain	2.9%	2.8%
Leg Pain	2.0%	1.2%
Cardiovascular		
Peripheral Edema	2.0%	1.2%
Digestive		
Dyspepsia	5.6%	4.9%
Diarrhea	4.0%	3.6%
Flatulence	3.4%	3.6%
Nausea	2.7%	3.2%
Constipation	1.8%	2.0%
Surgery	1.4%	3.6%
Musculoskeletal		
Arthralgia	6.7%	4.5%
Myalgia	2.7%	1.2%
Nervous		
Dizziness	2.5%	3.6%
Insomnia	2.2%	1.2%
Respiratory		
Rhinitis	13.2%	12.1%
Pharyngitis	12.0%	17.0%
Sinusitis	6.9%	5.7%
Cough Increased	2.7%	2.0%
Skin and Appendages		
Rash	3.4%	5.7%
Urogenital		
Urinary Tract Infection	1.6%	2.4%

The following effects have been reported with drugs in this class.
Skeletal: myopathy, muscle cramps, rhabdomyolysis, arthralgias, myalgia.
Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, vertigo, paresthesia, peripheral neuropathy, peripheral nerve palsy, anxiety, insomnia, depression, psychic disturbances.*Hypersensitivity Reactions:* An apparent hypersensitivity syndrome has been reported rarely that included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-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.

Post-Marketing Adverse Event Reports: The following events have been reported since market introduction. While these events were temporally associated with the use of BAYCOL® , a causal relationship to the use of BAYCOL® cannot be readily determined due to the spontaneous nature of reporting of medical events, and the lack of controls: hepatitis, myositis, rhabdomyolysis, some with associated renal failure (most cases involved concomitant gemfibrozil), urticaria, angioedema, visual disturbance, blurred vision.

Concomitant Therapy: In studies where cerivastatin sodium has been administered concomitantly with cholestyramine, no adverse reactions unique to this combination or in addition to those previously reported for this class of drugs were reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when HMG-CoA reductase inhibitors are used in combination with immunosuppressive drugs, fibric acid derivatives, erythromycin, azole antifungals or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended (*See* WARNINGS: *Skeletal Muscle*).

OVERDOSAGE

The maximum single oral dose of cerivastatin sodium received by healthy volunteers and patients is 0.4 mg.

No specific recommendations concerning the treatment of an overdosage can be made. Should an overdose occur, it should be treated symptomatically and supportive measures should be undertaken as required.

Dialysis of cerivastatin sodium is not expected to significantly enhance clearance since the drug is extensively (99%) bound to plasma proteins.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving cerivastatin sodium and should continue on this diet during treatment with cerivastatin sodium. (See NCEP Treatment Guidelines for details on dietary therapy.)

The recommended dose is 0.3 mg once daily in the evening. Cerivastatin sodium may be taken with or without food. The recommended starting dose in patients with significant renal impairment (creatinine clearance ≤60 mL/min/1.73m^2) is 0.2 mg once daily in the evening.

Since the maximal effect of cerivastatin sodium is seen within 4 weeks, lipid determinations should be performed at this time.

Concomitant Therapy: The lipid-lowering effects on LDL-C and Total-C are additive when cerivastatin sodium is combined with a bile-acid-binding resin. When co-administering cerivastatin sodium and a bile-acid-exchange resin, e.g., cholestyramine, cerivastatin sodium should be given at least 2 hours after the resin (*See also* ADVERSE REACTIONS: *Concomitant Therapy*).

Dosage in Patients with Renal Insufficiency: No dose adjustment is necessary for patients with mild renal dysfunction (Cl_{cr} 61-90 mL/min/1.73m^2). For patients with moderate or severe renal dysfunction, a starting dose of 0.2 mg is recommended (see CLINICAL PHARMACOLOGY - Special Populations - Renal).

HOW SUPPLIED

BAYCOL® (cerivastatin sodium tablets) is supplied as 0.2-mg, and 0.3-mg tablets. The different tablet strengths can be identified as follows:

Strength	Color	Markings	
		Front	Back
0.2 mg	light yellow	283	200 MCG
0.3 mg	yellow brown	284	300 MCG

BAYCOL® (cerivastatin sodium tablets) is supplied as follows:

Bottles of 100: 0.2 mg (NDC 0026-2883-51)
0.3 mg (NDC 0026-2884-51)

The tablets should be protected from moisture and stored below 77°F (25°C). Dispense in tight containers.

References:

1

Classification of Hyperlipoproteinemias

Type	Lipoproteins Elevated	Lipid Elevations	
		major	minor
I (rare)	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

C=cholesterol, TG=triglycerides, LDL=low-density lipoprotein,
VLDL= very-low-density lipoprotein, IDL=intermediate-density lipoprotein.

Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516 USA
Made in Germany

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020740/S03

STATISTICAL REVIEW(S)

Div File

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 18, 1998

FROM: Mathematical Statistician, Division of Biometrics II (HFD-715)

SUBJECT: Statistical Review not needed for this supplement

TO: File (NDA 20-740/013)

I talked to Dr. Orloff (HFD-510) about the need for a statistical review of the comparisons between 400 µg Baycol and 300 µg Baycol in trials 0149 and 0162. He stated that statistical superiority of 400 µg need not be demonstrated since the addition to the label simply informs the physician that it is reasonable to titrate a patient up to that level. No population-based inference about any "superior efficacy" of 400 µg is necessary. Consequently, he stated that a formal statistical review is not necessary.

APPEARS THIS WAY
ON ORIGINAL

/S/
David Hoberman, Ph.D.

Concur: Dr. Sahlroot /S/ 11/25/98

cc:
Orig. NDA #
HFD-510/division file, DOrloff, SSobel, SShen, MSimoneau
HFD-715/DHoberman, TSahlroot, division file, chron

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020740/S03

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JAN 14 1998 DF

JAN 14 1999

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20,740 (SNC-BB)	**SUBMISSION DATE: 12-23-97, 09-28-98**
BRAND NAME:	**Baycol**
GENERIC NAME:	**Cerivastatin**
REVIEWER:	**Xiaoxiong(Jim) Wei, Ph.D.**
SPONSOR:	**Bayer, West Haven, CT**
TYPE OF SUBMISSION:	**General correspondence**

Background: On December 23, 1997, the sponsor submitted to the Agency a general correspondence regarding the Agency's request to change the labeling in NDA 20,740 for cerivastatin to warn against use of cerivastatin with CYP3A4 substrates. The reason for the labeling change request is recent findings of rhabdomyolysis with some of statins and concomitant use of Posicor (mibefradil), which is CYP3A4 inhibitor. In this general correspondence, the sponsor submitted a summary and partial data from in vitro and in vivo drug-drug interaction studies. On September 28, 1998, the sponsor submitted a revised package insert to the Agency, which reflects some of the most recent findings in drug-drug interactions and drug adverse effects.

Study Summary:
In this submission, there are several studies involving both in vitro drug metabolism and in vivo drug interactions. In vitro studies, the sponsor has identified cerivastatin has two metabolic pathways which generate metabolites M1 and M23. CYP2C8 involves both metabolites formation whereas CYP3A4 only generates metabolite M1. Although Km of cerivastatin for CYP2C8 is about 3-4 fold (16.8 μM) lower than for CYP3A4 (64.7 μM), the intrinsic clearances ($Cl_{int}=K_m/V_{max}$) of CYP2C8 and CYP3A4 for cerivastatin are close, 0.034 and 0.027, respectively. The results from inhibitory effects of cerivastatin, M1 and M23 on CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6, and 3A4 showed that cerivastatin and M1 inhibited CYP2C8, CYP2C9, and CYP3A4. Metabolite M23 exhibited an inhibitory effect only on CYP2C8. In vivo studies, 3 days pretreatment of erythromycin (0.5 g tid) increased AUCs for cerivastatin and M23 21% and 57%, respectively, whereas 10 days pretreatment of erythromycin (0.5 g bid) increased AUC for cerivastatin up to 50%, Cmax to 24%. Itraconazole (200 mg qd for 10 days) increased AUC and T1/2 for cerivastatin 38% and 62%, respectively. AUC and T1/2 for M23 were increased to 51% and 78%, respectively. More importantly, cerivastatin also increased itraconazole AUC and T1/2 17% and 23%, respectively even though itraconazole has high affinity to CYP3A4. There are no significant drug-drug interactions between cerivastatin and cimetidine and nifedipine.

APPENDIX 1:

Title: CYP450 isoenzymes involved in the metabolism of cerivastatin in humans.
Study design: There are two major cerivastatin metabolites, M1 and M23. They are partially pharmacologically active (50% and 80% of parent compound, respectively).

Step 1: human liver microsomes incubation of cerivastatin with and without inhibitors. The details of experiments were not provided.
Result:

Table 1: Influence of different cytochrome P450 inhibitors on cerivastatin metabolism by human liver microsomes. Turnover of cerivastatin and formation of M-1 and M23 are given in percent compared to control.

Predominantly inhibited CYP	Inhibitor	Concentration	% Turnover of cerivastatin	Formation of M-1	Formation of M-23
1A2	Furafylline	20 μM + preincubation	101	105	98
	7,8-benzoflavone	1 μM	98	97	95
2A6	Diethyldithiocarbamate	100 μM + preincubation	66	80	56
	Coumarin	100 μM	98	99	95
	Tranylcypromine	0.5 μM	101	100	105
2C8	Quercetin	50 μM	44	56	37
	Taxol	20 μM	83	84	86
	Taxol	100 μM	44	47	46
2C9	sulfaphenazole	50 μM	98	93	103
2C19	Tranylcypromine	10 μM	97	98	94
	S(+)-mephenytoin	100 μM	102	101	95
2D6	quinidine	5 μM	96	99	100
2E1	4-methylpyrazole	200 μM	105	103	102
3A4	Troleandomycin	20 μM+ preincubation	86	80	100
	Troleandomycin	100 μM+ preincubation	81	72	99
	Ketoconazole	1 μM	91	88	101
	Ketoconazole	10 μM	67	62	86
All CYP	1-amino-1 H-benzotriazole	100 μM+ preincubation	3	6	0

Table 2: effects of isozyme selective inhibitors on turnover of M-1 and M23

Isoenzyme	Inhibitor	Concentration	Substrate M-1	Substrate M-23
2C8	Quercetin	50 μM	24	68
3A4	Troleandomycin	100 μM+ preincubation	74	29

Step 2: Human B-lymphoblastoid cell lines were used to further confirm CYP involvement.
Result: CYP2C8 metabolizes cerivastatin to both M-1 and M-23 to the similar extent, whereas the M-1 formation is mainly mediated by CYP3A4. Other CYP enzymes failed to metabolize cerivastatin.

Table3: Summary of enzyme kinetic parameters:

Expressed CYP	Parameter	M-1	M-23
2C8	Km	16.8 μM	14.3 μM
	Vmax	0.58 pmol/pmol CYP2C8	0.44 pmol/pmol CYP2C8
3A4	Km	64.7 μM	Non-detectable
	Vmax	1.72 pmol/pmol CYP3A4	

Reviewer's comments:

1. Since no details of experiments were provided, this reviewer can't comment on specific experimental procedures.
2. This reviewer agrees on the experimental approaches to determine metabolic pathways: human liver microsomal inhibition study plus cDNA expressed individual CYP enzymes.
3. Although Km of cerivastatin for CYP2C8 is about 3-4 fold (16.8 μM) lower than for CYP3A4 (64.7 μM), the intrinsic clearances ($Cl_{int}=K_m/V_{max}$) of CYP2C8 and CYP3A4 for cerivastatin is close, 0.034 and 0.027 μl/pmol/min, respectively.

APPENDIX 2:

Tittle: Determination of inhibitory potency of cerivastatin and its pharmacologically active metabolites M-1 and M-23 towards human P450 isozymes.
Study design: 8 recombinant CYP isozymes (1A2, 2A6, 2C8, 2C9, 2C19, 2D6, and 3A4) expressed in AHH cell lines were used in incubation experiments. Standard probe substrates were

used. The degree of inhibition of metabolite formation from standard probes was determined by comparison of the turnover in the absence and after addition of cerivastatin, M-1 or M-23. The potential inhibitors were used in 4-10 fold excess compared to the substrate concentrations. The calculation of the inhibitory effect was performed based on the following equations:

$i = [I]/\{[I] + Ki*(1+[S]/Km)\}$
Percent inhibition = 100*i
i = 1- % of control/100

Results:

Table 4: Inhibitory effects of **cerivastatin** on formation of metabolites of standard probes mediated by cytochrome P450 isozymes.

Isozyme	Substrate	Csubstrate [µM]	Cerivastatin [µM]	% of control	Calculated
CYP1A2	7-ethoxycoumarin	10	100.0	102.3	0.224
CYP2A6	Coumarin	2.0	100.1	101.8	0.242
CYP2C8	**Taxol**	**10**	**50.0**	**36.9**	**0.257**
CYP2C9-Arg	**Tolbutamide**	**48.0**	**200.2**	**30.3**	**0.584**
CYP2C19	S-Mephenytoin	42.8	200.2	96.8	0.479
CYP2D6-Val	Dextromethorphan	50	250.1	100.8	0.163
CYP2E1	Chlorzoxazone	51.3	250.1	116.2	0.615
CYP3A4	**Testosterone**	**49.5**	**250.0**	**67.6**	**0.607**

Table 5: Inhibitory effects of cerivastatin metabolite **M-1** on formation of metabolites of standard probes mediated by cytochrome P450 isozymes.

Isozyme	Substrate	Csubstrate [µM]	M-1 [µM]	% of control	Calculated
CYP1A2	7-ethoxycoumarin	10	100.0	94.5	0.224
CYP2A6	Coumarin	2.0	100.0	103.1	0.242
CYP2C8	**Taxol**	**10**	**50.0**	**60.2**	**0.257**
CYP2C9-Arg	**Tolbutamide**	**48.0**	**200.0**	**52.3**	**0.584**
CYP2C19	S-Mephenytoin	42.8	200.0	91.6	0.478
CYP2D6-Val	Dextromethorphan	50	250.0	93.0	0.163
CYP2E1	Chlorzoxazone	51.3	250.0	93.0	0.615
CYP3A4	**Testosterone**	**49.5**	**250.0**	**72.2**	**0.603**

Table 6: Inhibitory effects of cerivastatin metabolite **M-23** on formation of metabolites of standard probes mediated by cytochrome P450 isozymes.

Isozyme	Substrate	Csubstrate [µM]	M-23 [µM]	% of control	Calculated
CYP1A2	7-ethoxycoumarin	10.0	100.0	99.3	0.224
CYP2A6	Coumarin	2.0	100.0	100.1	0.242
CYP2C8	**Taxol**	**10.0**	**50.0**	**44.7**	**0.257**
CYP2C9-Arg	Tolbutamide	50.15	250.0	89.2	0.634
CYP2C19	S-Mephenytoin	42.8	200.0	96.6	0.478
CYP2D6-Val	Dextromethorphan	50.0	250.0	103.4	0.163
CYP2E1	Chlorzoxazone	51.3	250.0	100.9	0.615
CYP3A4	Testosterone	51.91	250.0	100.8	0.607

Table 8: Ki values towards cytochrome P-450 isoenzymes for Cerivastatin and its metabolites M-1 and M-23

Human CYP Isozyme	CYP2C8	CYP2C9	CYP3A4
Substrate	Taxol	Tolbutamide	Testosterone
Compound	Ki [μM]	Ki [μM]	Ki [μM]
Cerivastatin	13.6	104.9	258.7
M-1	15.0	n.i.	151.9
M-23	26.0	n.i.	n.i.

Sponsor's conclusion: From the in vitro results presented here it is inferred that cerivastatin and its major metabolites M-1 and M-23 are essentially no inhibitors of CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4.

Reviewer's comments:

1. This reviewer disagree with the sponsor's conclusion. Cerivastatin and its metabolites will exhibit inhibitory effects on CYP2C8, 2C9 and 3A4. The extent of inhibition may depend on relative molar concentrations of interacting substrate drugs of these CYP enzymes.
2. The equation for prediction was used to calculate in vitro inhibition for individual CYP enzymes. Surprisingly, the calculated inhibition was performed for all CYP enzymes. If there is no inhibitory effect on CYP enzymes by the compound, how could the inhibition be calculated? How to get Ki's for these non-inhibitory CYP enzymes?
3. Because cerivastatin inhibits tolbutamide metabolism, which mediated by CYP2C9, there are two possibilities: 1) cerivastatin inhibits CYP2C9 as a pure inhibitor without metabolism involvement and 2) substrate competition: additional metabolic pathways of cerivastatin may exist, which is mediated by CYP2C9.
4. The calculated inhibition using the equation is a valued approach. However, at the current stage, further validation is needed since the specificity of substrates is not exclusive for many CYP enzymes.

APPENDIX 3:

1. Cimetidine Interaction Study

Title: Investigation on the influence of cimetidine on the pharmacokinetics of cerivastatin.

Study design: Controlled, randomized, non-blind, crossover with single oral administration of cerivastatin (0.2 mg) with and without combined cimetidine treatment (0.4g, bid) of 31/2 days; a seven days washout interval between treatments. 7 subjects were enrolled.

PK analysis: AUC, Cmax, tmax, t1/2 were evaluated. ANOVA was performed for statistical analysis.

Result: No difference between two treatments.

2. Erythromycin Interaction Study

A. 3 Days Pretreatment of Erythromycin

Title: Influence of erythromycin on the PK of cerivastatin in 12 healthy male volunteers given a single oral dose of 300 μg cerivastatin after 3 days pretreatment with 3X500 mg erythromycin/day in a randomized non-blind, uncontrolled crossover study.

Study design: Randomized, non-blind, crossover with single oral administration of cerivastatin (0.3 mg) with and without combined erythromycin pretreatment (0.5g, tid) of 3 days; There was a seven days washout interval between treatments. 12 subjects were enrolled.

PK analysis: AUC, Cmax, tmax, t1/2 were evaluated. ANOVA was performed for statistical analysis.

Results:

Table 9: The changes in PK parameters of cerivastatin after three days pretreatment of erythromycin.

Compound	PK parameter	Cerivastatin + Erythromycin (Mean ± SD)	Cerivastatin alone (Mean ± SD)	Change (%)
Cerivastatin	AUC (μg*h)	17.78 ± 1.42	14.21±1.40	+21

[redacted]	Cmax (µg/L)	2.78 ± 1.43	2.46 ± 1.45	+13
	T1/2 (h)	2.98 ± 1.12	2.65 ± 1.27	+12
[redacted]	AUC (µg*h)	1.36 ± 2.36	3.11 ± 2.26	-56
	Cmax (µg/L)	0.19 ± 1.40	0.30 ± 2.20	-37
	T1/2 (h)	3.64 ± 3.01	3.99 ± 1.27	-9
[redacted]	AUC (µg*h)	5.89 ± 1.60	3.74 ± 1.49	+57
	Cmax (µg/L)	0.57 ± 1.43	0.39 ± 1.43	+46
	T1/2 (h)	4.95 ± 1.49	4.07 ± 1.44	+22

B. 10 Days Coadministration of Erythromycin

Title: A study to evaluate the potential reciprocal interaction between cerivastatin and erythromycin in hypercholesterolemic patients.

Study design: Non-randomized, non-blind multiple dose drug-drug interaction study with oral administration of cerivastatin (0.3 mg, qd from Day 1 to Day 19) and erythromycin treatment (0.5g, bid on Day –9 and from Day 6 through Day 16); 16 subjects were enrolled. PK sample collection: erythromycin: on Day –9 and Day 6; cerivastatin on Day 5 and Day 15. 16 subjects were enrolled.

PK analysis: AUC, Cmax, tmax, t1/2 were evaluated. ANOVA was performed for statistical analysis.

Results:

Table 10: The changes in PK parameters of cerivastatin after10 days concomitant administration of erythromycin.

Compound	PK parameter	Cerivastatin + Erythromycin (Mean)	Cerivastatin alone (Mean)	Change (%)
Cerivastatin	AUC (µg*h)	35.5	23.6	+50
	Cmax (µg/L)	4.6	3.7	+24
	T1/2 (h)	4.9	3.5	+40
[redacted]	AUC (µg*h)	Not available	Not available	Not available
	Cmax (µg/L)	0.27	0.30	-10
	T1/2 (h)	Not available	Not available	Not available
[redacted]	AUC (µg*h)	Not available	Not available	Not available
	Cmax (µg/L)	0.73	0.57	+28
	T1/2 (h)	Not available	Not available	Not available

Note: The PK parameters of erythromycin didn't change after concomitant treatment with cerivastatin.

Conclusions: Pre- and co-treatment of erythromycin 500 mg tid affects the metabolism of cerivastatin, administered as a single dose of 300 µg, to certain extent which is according to the statistical evaluation not of clinical relevance. The slight increase in half-life does not predict an accumulation beyond the known steady state behavior. The PK data for the metabolites further elucidate the CYP3A4 pathways involved in cerivastatin elimination. Based on the results of this study, there seem to be no necessity to adapt the steady-state dose of cerivastatin in hypercholesterolaemic patients when co-medicated with erythromycin.

Reviewer's comments:

This reviewer disagrees with the sponsor's conclusions because erythromycin increases plasma concentrations of cerivastatin and its metabolite, M-23 in a dose-dependent manner. The doses used in these studies were lower than regularly prescribed doses (0.5g qid, 2.0 g/day). Therefore, greater increase of plasma levels of cerivastatin and its metabolite, M-23 are expected in real clinical practice.

3. Itraconazole Interaction Study

Title: Summary of safety and PK data from study D97-011 multiple-dose interaction study of cerivastatin

and itraconazole in patients.

Study design: Non-randomized, non-blinded multiple dose drug-drug interaction study with oral administration of cerivastatin (0.3 mg, qpm from Day 1 to Day 19) and itraconazole (0.2 g qpm for 10 days from Day 6 to Day15). PK sample collection: on Day 6 and Day 15. 16 subjects were enrolled.

Result:

Table 11: The changes in PK parameters of cerivastatin, M-1 and M-23.

Compound	PK parameter	Cerivastatin + itraconazole (Mean ± SD)	Cerivastatin alone (Mean ± SD)	Change (%)
Cerivastatin	AUC (μg*h)	32.9	23.8	**+38**
	Cmax (μg/L)	5.5	4.6	**+20**
	T1/2 (h)	5.5	3.4	**+62**
M-1	AUC (μg*h)	1.64	1.73	-5
	Cmax (μg/L)	0.19	0.22	-16
	T1/2 (h)	5.1	5.4	-6
M-23	AUC (μg*h)	8.41	5.58	**+51**
	Cmax (μg/L)	0.76	0.58	**+31**
	T1/2 (h)	8.7	4.9	**+78**

Table 12: The changes in PK parameters of itraconazole.

Compound	PK parameter	Cerivastatin + itraconazole (Mean ± SD)	Itraconazole alone (Mean ± SD)	Change (%)
Itraconazole	AUC (μg*h)	1730.56	1482.50	+17
	Cmax (μg/L)	118.67	108.74	+9
	T1/2 (h)	14.75	11.95	+23

Table 13: The changes in PK parameters of 2-hydroxy-itraconazole.

Compound	PK parameter	Cerivastatin + itraconazole (Mean ± SD)	Itraconazole alone (Mean ± SD)	Change (%)
2-hydroxy-itraconazole	AUC (μg*h)	5669.9	4745.65	+19
	Cmax (μg/L)	229.15	199.86	+15
	T1/2 (h)	13.42	11.71	+15

Conclusions: These results indicate that itraconazole, a known potent inhibitor of CYP3A4, has a relatively small and consistent effect on the steady state pharmacokinetics of cerivastatin in patients with hypercholesterolemia. This less than 40% mean increase in cerivastatin plasma levels observed after 10 days of concurrent treatment is not expected to be clinically significant.

Reviewer's comments:

1. This reviewer disagrees with the sponsor's conclusion that the interaction of itraconazole and cerivastatin is not expected to be clinically significant because some patients may take up to 400 mg/day of itraconazole, which may generate greater increase of cerivastatin plasma concentrations.

2. Itraconazole also increases the values of all PK parameters of cerivastatin and its metabolite,M-23 such as AUC, Cmax, and T1/2.

3. Importantly, the fact that the inhibitory effect of cerivastatin on itraconazole was observed although these changes are minor. Caution should be taken when CYP3A4 substrate drugs are co-administered with cerivastatin, particularly when their plasma molar concentrations are lower than cerivastatin and their

therapeutic windows are narrow. Another important fact is that the ratio of [I]/Ki for cerivastatin is almost negligible or Ki value is more than 26,500 times [I] (Ki=258.7 μM from Table 8 and [I] = Cmax=4.6 – 5.5 μg/L =0.0096 μM from Table 11, MW=481.5). No drug-drug interactions would be expected based on these in vitro and in vivo data if the equation for in vitro/in vivo predictions is applied. Therefore, the validation of in vitro and in vivo correlation should be further emphasized.

4.Nifedipine Interaction Study
Title: Randomized, non-blind, 3-fold crossover study to investigate the influence of a simultaneous single dose administration of 60 mg nifedipine GITS and 300 μg cerivastatin on the pharmacokinetic properties of each drug in 18 healthy male subjects.
Study design: Randomized, non-blind, single dose study with 3 study periods of 3 days each with a washout phase of 7 days. 18 subjects were enrolled.
PK analysis: AUC, Cmax, tmax, t1/2 were evaluated. ANOVA was performed for statistical analysis.
Result: No difference between two treatments.

COMMENTS TO BE SENT TO SPONSOR

1.Erythromycin does cause the increase in Cmax and T1/2 of cerivastatin in a dose–dependent manner. The greater interaction will be expected in real medical practice since the regularly prescribed dose is 0.5 g, qid or 2.0g/day (0.5 g bid or 1.0 g/day was used in 10 days drug interaction study). Particularly, rare cases of rhabdomyolysis have been reported with cerivastatin, which is severe and can be fatal. Therefore, Caution should be taken when CYP3A4 substrate drugs are co-administered.

2.The results from drug-drug interaction study between cerivastatin and itraconazole show that cerivastatin has potential to cause drug-drug interactions with the concomitant administration of other CYP3A4 substrate drugs, particularly when their plasma molar concentrations are similar to or lower than levels of cerivastatin and their therapeutic windows are narrow.

3.In Appendix 2, the equation used to calculate inhibition for individual CYP enzymes was for in vitro prediction. Surprisingly, the calculated inhibition was performed for all CYP enzymes. If there is no inhibitory effect on CYP enzymes by the compound, how could the inhibition be calculated? How to get Ki's for these non-inhibitory CYP enzymes? Since cerivastatin inhibits tolbutamide metabolism, which mediated by CYP2C9, there are two possibilities: 1) cerivastatin inhibits CYP2C9 as a pure inhibitor without metabolism involvement and 2) substrate competition: additional metabolic pathways of cerivastatin may exist, which is mediated by CYP2C9.

LABELING COMMENTS (to be sent to the sponsor):

(~~Strikeout text~~ should be removed from labeling; Double underlined text should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the general correspondence for NDA 20740 (cerivastatin) submitted on 12-23-97 and revised package insert submitted on 09-28-98. The opinion of OCPB is that potential harmful drug-drug interactions between cerivastatin and other CYP3A4 substrate drugs do exist. This recommendation, comments and labeling comments on page 7 should be sent to the sponsor as appropriate.

/S/

Xiaoxiong (Jim) Wei, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

APPEARS THIS WAY
ON ORIGINAL

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 1/14/99

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 1/14/99

CC: NDA 20740 (orig.,1 copy), HFD-510(Simoneau, Orloff), HFD-850 (Lesko, Huang), HFD-870(Wei, Ahn, M. Chen), CDR (Barbara Murphy).

Code: IR

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020740/S03

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

APPROVED

Labeling Review

Application Number: NDA 20-740/S-003

Name of Drug: Baycol (cerivastatin sodium) Tablets

Sponsor: Bayer Corporation

Materials Reviewed: June 26, 1997 last approved labeling and September 28, 1998 revised draft labeling for supplement-003.

Background and Summary Description: Supplement-003 was a SPECIAL SUPPLEMENT "Changes Being Effected. The changes in the package insert to the CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the Baycol package insert. Specific changes are noted in the approval letter for supplement-003.

A labeling review was done of the August 31, 1998 submission and the sponsor was contacted to make the corrections. In the "HOW SUPPLIED" section the notation [redacted] was deleted and the color for the 0.3 mg tablet was corrected from [redacted] to [redacted]. These corrections were submitted September 28, 1998.

For supplement-003, the reviewing team has accepted the labeling changes in submission dated September 28, 1998 (Bayer Draft "Revised: 28 September, 1998").

Medical Team Leader /S/ 11-24-98

Pharmacology Team Leader /S/ 11/30/98

Chemistry Reviewer /S/ 11/25/98

Chemistry Team Leader /S/ 11/24/98

Biopharm Team Leader /S/ 11/24/98

Chief, Project Manager /S/ 12/3/98

Project Manager /S/ Nov 24, 1998

cc:Original NDA 20-740-S003
DivFile

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20-740
Div File

MEMORANDUM

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: OCT 13 1998

FROM: Lanh Green, R.Ph., M.P.H.
Reports Evaluation Branch, HFD-735

/S/ for Ralph Lillie 10/2/98

THROUGH: Ralph Lillie, R.Ph., M.P.H., Acting Director
Division of Pharmacovigilance and Epidemiology, HFD-730

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

SUBJECT: Review of Hepatic Tumors Reported with HMG-CoA Reductase Inhibitors

Dr. Mary Parks had a concern about three cases of hepatic carcinomas seen in the treatment arm of a randomized double-blind, placebo-controlled study (AFCAPS/TexCAPS, protocol #042) for lovastatin. She asked me to search the Adverse Event Reporting System for reports of hepatic neoplasms reported with six marketed HMG-CoA reductase inhibitors: atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. The following is a summary of the reported cases of hepatic tumors, benign and malignant, to the Adverse Event Reporting System (AERS) database.

Background

Currently, there are six HMG CoA reductase inhibitors (HMG) marketed in the U.S. The dates of approval for these six HMGs follow:

08/87	lovastatin - Mevacor
10/91	pravastatin - Pravachol
12/91	simvastatin - Zocor
12/93	fluvastatin - Lescol
12/96	atorvastatin – Lipitor
06/97	cerivastatin - Baycol

Hepatoma is a labeled event in the Adverse Reactions section for all six HMG-CoA reductase inhibitors. In the Precautions section and *Carcinogenesis, Mutagenesis, Impairment of Fertility* sub-section, each HMG has a variation of a paragraph describing animal experiences related to hepatoma. Because lovastatin was the first HMG marketed in 1987, and also received the highest number of reports of hepatic neoplasms, its labeling is used as an example for this paragraph:

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 500mg/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 100mg/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 Mevacor.)...

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)...

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...

Spontaneous Case Reports

From marketing to September 2, 1998, a total of 51 reports of hepatic neoplasms, US and foreign, were identified in AERS database. The attached tables 1-5 list reports and selected characteristics for only four of the six HMGs: 1)atorvastatin, 2)lovastatin, 3)pravastatin, and 4)simvastatin. Cerivastatin and fluvastatin did not have any hepatic neoplasm reports. There were 12 fatalities (24% of total). Of these 12 reports of fatal outcome, eight were from foreign countries.

Table 1. Counts of these 51 reports by drug, reporting source, and fatality

	Approval Date	U.S.	Foreign	Total
Atorvastatin	12/96	2 (1 fatal)	0	2 (1 fatal)
Lovastatin	08/87	25 (3 fatal)	2 (2 fatal)	27 (5 fatal)
Pravastatin	10/91	6	0	6
Simvastatin	12/91	2	14 (6 fatal)	17 (6 fatal)
Total		**35 (4 fatal)**	**16 (8 fatal)**	**51 (12 fatal)**

Table 2. Counts of hepatic tumor status for these 51 reports by drug and source

Tumor Status		Malignant		Benign		Unknown	
	N	US	Foreign	US	Foreign	US	Foreign
Atorvastatin	2	2	0	0	0	0	0
Lovastatin	27	15	2	7	0	3	0
Pravastatin	6	4	0	1	0	1	0
Simvastatin	16	2	13	0	1	0	0
Total	51	23	15	8	1	4	0

Drug Use Data

Drug use data are estimated from the total prescriptions and new prescriptions dispensed for the six HMGs for the years 1993 through July 1998, and data on the age and gender distribution are from the National Disease and Therapeutic Index for the years 1992 through July 1998.

From the drug use data in the US, atorvastatin is the leading HMG sold in 1998 with an estimated _____ total and _____ new prescriptions sold through July 1998. In 1997, simvastatin had the highest total prescriptions sold estimated at _____ and new prescriptions at _____

Looking at the use data of the six HMGs by age and gender, the range is estimated to be 13-16% more drug use in male than female patients aged 40 to 59 years; the use is about equal among women and men aged 60-64 years; then, the trend of the range reverses to 5-9% more drug use in female than male patients aged 65-74 years.

Medline Search

Medical literature did not reveal any published cases of HMG associated carcinoma of the liver.

Incidence of Primary Cancer of liver

In the US populations covered by the Surveillance, Epidemiology, and End Results (SEER) program, the age-adjusted incidence of hepatocellular carcinomas (HCC) rose slightly from 1.3 to 1.5 cases per 100,000 population from 1973 to 1987. The age-adjusted incidence of intrahepatic cholangiocarcinoma was 0.4 per 100,000.[1] However, the incidence for Far East Asians and Sub-Sahara Africans is 500 cases per 100,000 population, because of their higher rate of exposure to hepatitis B and C viral infections.[2] Primary cancers of the liver occur most commonly as hepatocellular carcinomas (67.5%).[3] Intrahepatic cholangiocarcinomas (19.1%) rank second, followed by heptatoblastoma and angiosarcoma. HCC occurred more frequently in men than women (4:1) and in African Americans than Whites (2:1).[4,5]

In the US (SEER program), Figure 1 below shows that the incidence rate per 100,000 for male patients having hepatocellular carcinoma steadily climbed, starting at age 44, at 1.5, and peaked at age 84 at 15.7 cases; the rate for ages 65-69 was at 12 per 100,000.[1]

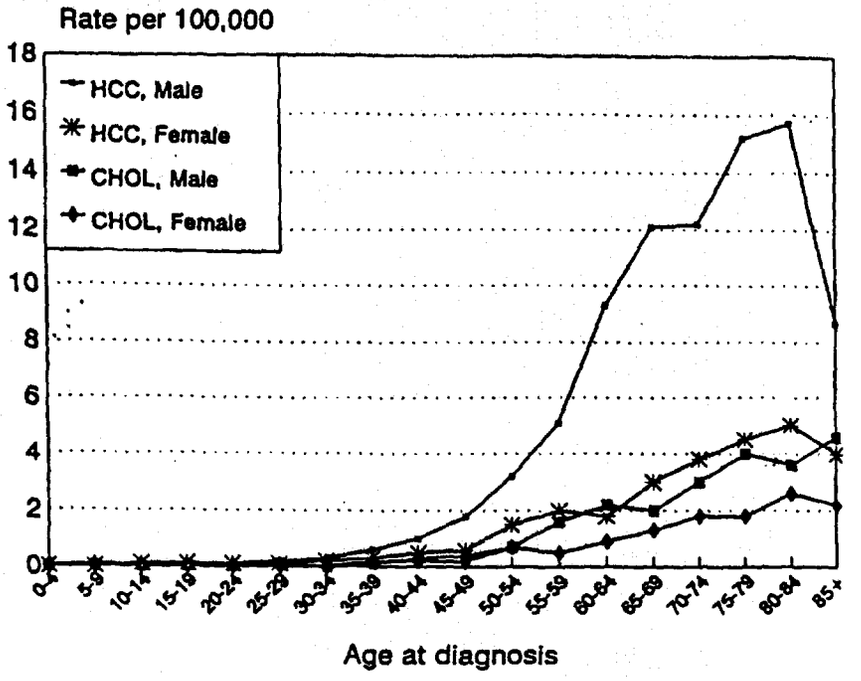

Figure 1. Liver and intrahepatic bile ducts: age-specific incidence rates by histologic subtype and sex according to the SEER data for 1983–1987. HCC: hepatocellular carcinoma. CHOL: cholangiocarcinoma.

Summary

For all six HMG-CoA reductase inhibitors, hepatoma is a labeled adverse event. The fact that it is a labeled event may account for the scant information found in the majority of the submitted reports.

US Reports

Of the 35 US reports, 23 patients had malignant tumors, 8 had benign tumors, and 4 had tumors with undetermined status of malignancy. There were 4 fatalities. Among the 23 patients described as having malignancy, only 7 malignancies were clinically documented: hepatocellular carcinoma (1), hepatic carcinomas with unknown primary site (3); secondary liver metastasis from other primary sources (3). The remaining 16 patients had undocumented diagnoses: cholangiocarcinomas (3), hepatic carcinomas with unspecified primary site (11), combined liver and pancreas carcinomas (1), and combined liver and colon carcinomas (1). By contrast, all eight patients with benign hepatic mass had a clinically documented diagnosis.

The selected demographics show that the median patient age for all six HMGs was 65 years (range=39-79); there were slightly more males than females (16:12), 7 patients had unknown gender; the median onset time to diagnosis was 12 months (range=0.5-132).

Foreign Reports

Of the 16 foreign reports, 15 patients had clinically documented diagnoses: primary hepatocellular carcinomas (3), cholangiocarcinomas (2), hepatic carcinomas with unknown or unspecified primary site (7), hepatoma metastasized to bone (1), and secondary liver metastasis from lung and skin (1). The last case was a malignant liver carcinoma not documented clinically. Two patients had confounding risk factors such as liver cirrhosis and hepatitis C viral infection.

Long-term HMG Exposure

Among the 22 clinically documented malignancies, 2 patients were treated with HMG therapies for longer than five years. They are described below:

1) A 66 year-old woman from Tennessee who took lovastatin for about 11 years developed a large mass in the liver, measured at 16 cm. Lovastatin was discontinued. Her tumor was resected. Histopathology of the liver resection found a well circumscribed hepatocellular carcinoma with no evidence of vascular invasion. She recovered and was doing well one month after surgery.

2) A 50 year-old man from the United Kingdom who participated in a 6-month simvastatin study (Protocol 905-1A) prior to the initiation of therapy was diagnosed with metastatic liver cancer after nine years of continued therapy. The report contained limited information, and follow-up had been requested but not yet received. At the time of diagnosis, the primary site was not found yet.

Conclusion

In a study covering the period from 1983-1987, primary liver cancers occurred rarely in the US, the age-adjusted incidence being estimated at 1.5 cases per 100,000 population. However, for male patients aged 65, the rate increased to 12 per 100,000 for hepatocellular carcinoma. In addition, carcinomas of the liver and intrahepatic bile ducts occurred primarily in the elderly population. Greater than 85% of carcinomas occurred in individuals aged 50 years and older.[1] At the present time, the population treated with lipid lowering agents is also an older population, and the median age in patients who experienced hepatic carcinomas with the use of HMGs within AERS was 65 years.

Taking into account the latent onset time of cancer, the underreporting of adverse events, and the limited documentation in most of the submitted reports, it is difficult to assess the estimated reporting rate of primary liver cancer within AERS to compare it with the background rate. However, the animal hepatic tumors that were mentioned in the labeling for HMGs, the two patients who developed hepatic cancer after long-term lovastatin and simvastatin therapy, and the malignant hepatic neoplasm that was diagnosed in three study patients in the AFCAPS/TexCAPS study raise our concern about the potential increase in carcinogenic effect of the HMGs on liver.

/S/

Lanh Green, RPh, MPH

Concur: /S/

Toni Piazza-Hepp, PharmD, Group Leader

cc:

HF-2	Goldman/Kennedy
HFD-510	Orloff/Parks/Simoneau/Stadel/NDA
HFD-730	O'Neill /S/
HFD-733	Rodrig...ysowski
HFD-735	Chen/Hepp/Chron/Consult/Green

References

1. Carriaga MT et al. Cancer suppl.1995;75(1):174.
2. Isselbacher KJ et al. Tumors of the liver. Harrison's Principles of Internal Medicine, 13th ed. McGraw-Hill, Inc. 1994.
3. Carriaga MT et al. Cancer suppl.1995;75(1):173.
4. Ries LAG, et al. Cancer statistics review 1973-1988. Bethesda (MD): National Cancer Institute, 1991.
5. Craig JR et al. Tumors of the liver and extrahepatic bile ducts. In: Altalas of tumor pathology. 2nd series, fascicle 26. Washington (DC): Armed Forces Institute of Pathology, 1989.

Table 1. Hepatic Neoplasms Reported with Use of Atorvastatin and Simvastatin in The U.S.

case #	id	location	age	sex	dose mg/d	other lipid med	comeds	onset time at dx, mo	presentation	diagnosis	documented dx	malignancy	outcome/cause of death
Atorvastatin/Lipitor													
1	M078251	CA		m		pravastatin (5 mo)		1.5	nausea, abdo pain	hepatic & pancreatic CA	n	y	died/liver failure
2	-970967	MI		f				1.5	abdo pain, abnorm LFTs	hepatic CA	y	y	hospitalized
Simvastatin/Zocor													
1	97031857	MI	65	f	10			38	malaise, jaundice, inc. LFTs	CA of ampulla of Vater	n	y	hospitalized
2	95101444	TX	67	m				24		liver tumors	n	y	hospitalized

Table 1. Hepatic Neoplasms Reported with T e of Atorvastatin and Simvastatin in The U.S.

case #	others
Atorvastati	
1	consumer report
2	u/s= normal gallbladder
Simvastatin	
1	consumer report, no f/u.
2	consumer report, f/u.requested but not obtained. Colon CA dx 1 year p/Rx; resection of colon.

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Table 2. Hepatic Neoplasms Repo[illegible]th The Use of Lovastatin in The U.S.

case #	id	location	age	sex	dose mg/d	other lipid med	comeds	onset time at dx, mo	presentation	diagnosis	documented dx	malignancy
Lovastatin/Mevacor												
1	94100973	NE	72	m						hepatic CA	n	y
2	94061236	FL	79	m		no	aspirin, stool softener		anorexia, malaise, weight loss	cholangiocarcinoma metastatic to liver, no jaundice	y	y
3	94081689	TN		m						hepatic CA	n	y
4	51225	IL	39	f		gemfibrozil (previous Rx)	Darvocet, Tavist	10	hepatic tumor discovered during tubal ligation	biopsy:benign focal nodular hyperplasia w/inflmmatory reaction	y	n
5	89100603	TX	50	m	20	no	Lopressor, Sorbitrate	1	fever, abdo pain	u/s hepatic mass, biopsy: steatosis	y	n
6	90080463	MI	53	f	20	no	Premarin	10	RUQ pain	CT scan: hepatoma	y	y
7	95020371	MN	53	f	20	no	estrogen, progesterone, Naprosyn	15	ataxia, myopathy	liver tumor was mentioned but not worked up	y	
8	92120355	WI	56	f	20			13	abnormal LFTs	CT scan: possible hepatic tumor	y	n
9	92120355	CA	65	m	20	niacin	Anaprox	12	hemangioma in the liver was dixcovered during a CT scan of kidney studies	atypical hemangioma. U/S showed enlargement of lesion 2 months later.	y	n
10	96090981	TN	66	f	40			132	epigastric pain, wgt loss	biopsy: hepatocellular carcinoma	y	y
11	95010672	NJ	66	f	80			96	multiple ADRs	"liver cancer"	n	y
12	91070615	IL	71	m	20			0.5	abnormal LFTs	"nodules" in the liver; suggestive of metastatic lesions	y	y
13	93110867	PA	71	f	20			12	severe arm pain	CT scan: liver tumor	y	
14	94090508	USA	74	m	40	gemfibrozil (previous Rx)	none	24		liver CA	n	y

Table 2. Hepatic Neoplasms Repo. th The Use of Lovastatin in The U.S.

case # Lovastati	outcome/cause of death	others
1	died	consumer report
2	died 2 wks p/dx	no autopsy; unknown primary site possibly related to bile duct CA
3	died	consumer report
4	hospitalized	OC (co-suspect d/c before starting Rx ; unknown name, dose, & duration)
5	non-hospitalized	recovered
6	hospitalized	metastasis to rt chest and spine
7	non-hospitalized	A battery of tests was performed to determine the etiology of her symptoms but none was done for liver tumor.
8	non-hospitalized	Biopsy showed fatty change & no malignancy. F/u CT scan showed no change 3 months later.
9	non-hospitalized	no f/u.
10	hospitalized	surgical removal of tumor Pathology: hepatic CA w/ no vascular invasion; normal gallbladder
11	non-hospitalized	consumer report; other ADRs included pituitary gland tumor, melanoma, memory loss, heart valve replacement, discolored buccal mucous membrane which matched the color of Rx tablet; no f/u from clinician.
12	non-hospitalized	carcinoma of the tonsils found during a vestibulotomy prior to Rx initiation.
13	non-hospitalized	malignancy not determined
14	non-hospitalized	Patient Support Program sponsored by Merck Marketing Div. No f/u.

Table 2. Hepatic Neoplasms Repor h The Use of Lovastatin in The U.S.

case #	id	location	age	sex	dose mg/d	other lipid med	comeds	onset time at dx, mo	presentation	diagnosis	documented dx	malignancy
15	95010058	PA	75	f					liver and gallbladder mass	no f/u	n	
16	51642	NY								CT scan: liver tumor	y	
17	89070763	TX		m		no	none		liver CA		n	y
18	92040864	OK		f					GGTP inc. by 50%	benign nodular hyperplasia	y	n
19	92050610	TX			40				liver mass	biopsy:focal nodular hyperplasia	y	n
20	94100782	USA		m						bile duct CA	n	y
21	94100702	USA		m						bile duct CA	n	y
22	94101018	TX		m						liver CA	n	y
23	95010175	TX								liver CA	n	y
24	95070126	PA		m	40					liver and colon CA	n	y
25	96050526	USA				pravastatin (unknown duration)		12		liver CA	n	y
Demographics		N=25	age	female	dose	no lipid med	no other DM Rx	onset time at dx, mo			yes	yes
		average	63.6	9	31.7	5	2	28.1			13	15
Blank= unknown		median	66.0	male	20.0	other lipid med		12.0			no	no
		range		12		4					12	6
		minimum										
		maximum										
			unknown age 11		unknown dose 13			unknown onset time 13				

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Table 2. Hepatic Neoplasms Repo th The Use of Lovastatin in The U.S.

case #	outcome/cause of death	others
15	non-hospitalized	consumer report
16	non-hospitalized	malignancy not determined, no f/u
17	non-hospitalized	consumer report
18	non-hospitalized	co-suspect: estrogens; no f/u
19	non-hospitalized	normal LFTs except for elevated GGTP
20	non-hospitalized	consumer report, no f/u
21	non-hospitalized	consumer report, reporter refused to provide f/u
22	non-hospitalized	consumer report, no f/u
23	non-hospitalized	f/u requested but not received
24	non-hospitalized	consumer report, f/u requested but not received
25	non-hospitalized	consumer report

Demogra	died = 3	
	hospitalized = 3	
Blank= unknown	non-hospitalized	
	19	

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Table 3. Hepatic Neoplasms Repor h The Use of Pravastatin in The U.S.

case #	id	location	age	sex	dose mg/d	other lipid med	comeds	onset time at dx, mo	presentation	diagnosis	documented dx	malignancy
Pravastatin/Pravachol												
1	M035466	NY	54	m	20	no	Normodyne, vitamins	10	abdo pain, abnorm LFTs	CT scan: 2 nodules in liver	y	
2	M026486	SC	64	m	20	no	Pepcid, Lopressor, Zestril	2.5	generalized aching	biopsy: liver CA, primary site: lung CA	y	y
3	M078053	OR	65	f	20	no	aspirin, Lozol, Zestril	12		u/s benign hepatic tumor	y	n
4	M47884	TX								liver CA	n	y
5	M047936	TX								liver CA	n	y
6	M047935	TX								liver CA	n	y
Demographics		N=6	age	female	dose	no lipid med	no other DM Rx	onset time at dx, mo			yes	yes
		average	61.0	1	20.0	3	0	8.2			3	4
Blank= unknown		median	64.0	male	20.0	other lipid med		10.0			no	no
		range		2		5					3	1
		minimum	54	unknown	20	unknown	unknown	2.5				unknown
		maximum	65	3	20	4	4	12				1
			unknown age		unknown dose			unknown onset time				
			3		3			3				

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Table 3. Hepatic Neoplasms Repo. .th The Use of Pravastatin in The U.S.

case #	outcome/cause of death	others
Pravastati		
1	non-hospitalized	consumer report, malignancy not mentioned
2	hospitalized	one month p/Rx: normal LFTs; 2.5 mo p/Rx: SGPT=1000, SGOT=500, Bili=3.5 . Died 8 days p/liver biopsy
3	non-hospitalized	consumer report
4	non-hospitalized	A physician reported that 4 of his friends were take pravastatin (3) and lovastatin (1) and developed liver cancer. However, he could not provide any additional information about his friends' adverse events.
5	non-hospitalized	same as above
6	non-hospitalized	same as above
Demogra	hospitalized	
	1	
Blank= unknown	non-hospitalized	
	5	

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ON ORIGINAL

Table 4. Hepatic Neoplasms Reported ı ıe Use of Lovastatin in Foreign Countries

case #	id	location	age	sex	dose mg/d	other lipid med	comeds	onset time at dx, mo	presentation	diagnosis	documented dx
Lovastatin/Mevacor											
1	92085532	Germany	46	m	20	no			hepatic tumors	intrahepatic metastasized cholangiocarcinoma	y
2	92115537	Germany	70	m	80	no	cloprednol (co-suspect), ramipril, nitrendipine, piretanide	3	asymptomatic	u/s- liver metastasis, biopsy- small-cell bronchial neoplasm, amelanotic melanoma	y

Table 4. Hepatic Neoplasms Reported ne Use of Lovastatin in Foreign Countries

case #	outcome/cause of death	others
Lovastati		
1	died 1 month p/dx	unknown duration of therapy, but Rx was initiated 3.3 years before death
2	died <1 month p/d/c Rx therapy	

Table 5. Hepatic Neoplasms Reported \ ıe Use of Simvastatin in Foreign Countries

case #	id	location	age	sex	dose mg/d	other lipid med	comeds	onset time at dx, mo	presentation	diagnosis	documented dx	malignancy
Simvastatin/Zocor												
1	97057852	Austria	52	m	20	benzafibrate (? duration)	Lisinopril, famotidine, metoprolol, citalopram, aspirin, dexamethasone	1	headache, brain disorder, apraxia	cerebral and hepatic metastasis (primary site- possibly lung CA)	y	y
2	90070590	France	60	f	20			6	jaundice, incr. LFTs	biopsy:liver metastasis, thrombosis	y	y
3	92070854	Switzerland	66	m	20	no	none	24		CT scan & biopsy: liver CA	y	y
4	95037512	Belgium	67	m	20	benzafibrate (? duration)	metformin, isosorbide, dipyridamole,	7		liver CA	y	y
5	971015027	UK	74	m	10	no	nifedipine, aspirin,	12		hepatoma	y	y
6	96035140	UK		m	10	no	atenolol, isosorbide, aspirin	6		hep. C, hepatocellular CA	y	y
7	92020971	Australia	46	m		no	none		fever, jaundice, RUQ pain	CT scan:fluid filled, necrotic center tumor in liver	y	
8	94060446	Germany	53	m	20	no	isosorbide, naftidrofuryl	20	asymptomatic	u/s liver mass, biospy: benign tumor	y	n
9	92020033	Australia	68	m	10	no	Elavil (co-suspect), Captopril lorazeam	3	elevated LFTs	CT scan & biopsy: liver CA	y	y
10	94066034	France	68	m	10	no	celiprolol, diltiazemaspirin trmetazidine	16	"primitive" liver CA		y	y
11	97105064	UK	74	f		no	no	48	bile duct CA		y	y
12	95036009	France	80	m	20	no	atenolol, nifedipine, naftidrofuryl, carbutamide	10	inc. LFTs	primitive liver CA	y	y
13	97075094	UK	50	m				108	metastatic liver CA	primary site not yet found	y	y

Table 5. Hepatic Neoplasms Reported \ e Use of Simvastatin in Foreign Countries

case #	outcome/cause of death	others
Simvastat		
1	died	Cause of death: multi-organ metastasis (lung, brain, liver, mouth); died 4 months p/stopping simvastatin
2	died	no autopsy
3	died	simvastatin was discontinued for unknown reasons; died 40 days after dx of hepatic CA; primary site not found and no autopsy
4	died	cause of death: hepatic carcinoma. Three attempts to obtain f/u were unsuccessful.
5	died	normal LFTs 1 month p/initiation of Rx; no hx of alcohol abuse, negative HBV, no autopsy.
6	died	Budd-Chiari syndrome
7	hospitalized	malignancy not determined
8	hospitalized	u/s showed a smaller and less dense tumor one month p/d/c Rx.
9	hospitalized	no f/u
10	unknown	f/u requested but not received
11	hospitalized	no f/u
12	hospitalized	LFTs returned to normal one month after stopping Rx. Hepatic CA was discovered 2 years p/ d/c Rx, and O4metastasized to bone.
13	unknown	patient was in study for 6 months (protocol 905-1A) prior to the initiation of simvastatin; f/u was requested but not received.

Table 5. Hepatic Neoplasms Reported v e Use of Simvastatin in Foreign Countries

case #	id	location	age	sex	dose mg/d	other lipid med	comeds	onset time at dx, mo	presentation	diagnosis	documented dx	malignancy
14	94107925	Canada			10	no	aspirin	8	swollen ankle	asymptomatic liver CA	n	y
Demographics		N=14	age	female	dose	no lipid med	no other comeds	onset time at dx, mo			yes	yes
Blank= unknown		average	63.2	2	15.5	10	2	20.7			13	12
		median	66.5	male	20.0			10.0			no	no
		range		11							1	1
		minimum	46	unknown	10	unknown	unknown	1			unknown	unknown
		maximum	80	1	20	2	2	108			0	1

Table 5. Hepatic Neoplasms Reported \ ıe Use of Simvastatin in Foreign Countries

case #	outcome/cause of death	others
14	unknown	f/u requested but not received
Demogra Blank= unknown	died 6 hospitalized 5 unknown 3	

19062

Bayer

Pharmaceutical Division

9807428

Bayer Corporation
400 Morgan Lane
West Haven, CT 06516-4175
Phone: 203 812-2000

August 31, 1998

Solomon Sobel, MD, Director
Division of Metabolism and Endocrine Drug Products
Office of Drug Evaluation II HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-740
BAYCOL™ (cerivastatin sodium tablets)
Amendment to Supplement S-003 (7/21/98)

Dear Dr. Sobel,

On June 21, 1998 Bayer Corporation Pharmaceutical Division is submitted a "Special Supplement - Changes Being Effected" for BAYCOL™ (cerivastatin sodium tablets). At this time Bayer is submitting an amendment to that supplement.

At the request of FDA, the following text section - Precautions - Drug Interactions - Other Concomitant Therapy is being deleted.

OTHER CONCOMITANT THERAPY: Although specific interaction studies were not performed, in clinical studies, cerivastatin sodium was used concomitantly with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, calcium-channel blockers, diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant adverse interactions.

The changes in the package insert, which are highlighted in the attached copy of the revised package insert also include the following changes which were included in our previous submission:

WARNINGS - Skeletal Muscle
Change wording from -

To:

Addition of the following section:

Additionally, the following minor corrections were made:

In the Pharmacokinetics: Metabolism sections was changed to which is the correct terminology for the compound.

In Table 2 - NCEP Treatment Guidelines:
The last entry in the "Goal" column was corrected from: " "
to "

Included in this submission is a diskette containing an electronic version of this labeling.

If there are any questions regarding this submission please contact me at (203) 812-2615.

Sincerely,

for

APPEARS THIS WAY
ON ORIGINAL

Nancy C. Motola, Ph.D.
Deputy Director, Regulatory Affairs

/fks

Attachment

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-740/S-003

AUG - 5 1998

Bayer Corporation Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516-4175

Attention: Nancy C. Motola, Ph.D.
Deputy Director, Regulatory Affairs

Dear Dr. Motola:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: BAYCOL (cerivastatin sodium tablets)

NDA Number: 20-740

Supplement Number: S-003

Date of Supplement: July 21, 1998

Date of Receipt: July 22, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 20, 1998, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research