CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-740/S006

APPROVAL LETTER

NDA 20-740/S-006

Bayer Pharmaceutical Division
Attention: Frederich K. Sundermann
Deputy Director, Regulatory Affairs
400 Morgan Lane
West Haven, CT 06516-4175

30 MAR 2001

Dear Mr. Sundermann:

Please refer to your supplemental new drug application dated August 3, 1999, received August 4, 1999, 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 February 2 and 6, 2001.

This supplemental new drug application provides for revisions to the Package Insert to include information on the metabolism of cerivastatin and the formation of its metabolites under the Metabolism subsection of the **CLINICAL PHARMACOLOGY** section. In addition, the results of the drug interaction studies involving omeprazole and cyclosporine will be included in the Drug Interactions subsection of the **PRECAUTIONS** section of the Package Insert. The specific changes are as follows:

To the **CLINICAL PHARMACOLOGY, Metabolism** section, the following paragraph has been added:

> *In Vitro* studies show that the hepatic cytochrome P450 (CYP) enzyme system catalyzes the cerivastatin biotransformation reactions. Specifically, two P450 enzyme sub-classes are involved. The first is CYP 2C8, which leads predominately to the major active metabolite, M23, and to a lesser extent, the other active metabolite, M1. The second is CYP 3A4, which primarily contributes to the formation of the less abundant metabolite, M1. The CYP 3A4 enzyme sub-class is also involved in the metabolism of a significant number of common drugs. The potential importance of the dual pathway hepatic metabolism of cerivastatin as a protective mechanism is shown in clinical studies examining the effect of the known potent CYP 3A4 inhibitors, erythromycin and itraconazole. In these interaction studies, specific inhibition of the CYP 3A4 enzyme sub-class resulted in a minimal 1.4- to 1.5-fold mean increase in cerivastatin plasma levels following co-treatment with erythromycin or itraconazole, possibly because of effective metabolism via the alternate CYP 2C8 pathway.

To the **PRECAUTIONS, Drug Interactions** section, the following statements have been added:

> **OMEPRAZOLE:** There were no changes in the pharmacokinetic parameters of either cerivastatin or its major active metabolites, or in omeprazole in healthy young males given single 0.3 mg oral doses of cerivastatin alone or on the fifth day of a five-day omeprazole 20 mg daily pre-treatment.
>
> **CYCLOSPORINE**: The single dose pharmacokinetics of 0.2 mg of cerivastatin in healthy subjects was compared to single and multiple doses in renal transplant patients who were at steady-state with respect to cyclosporine. Cyclosporine levels were unaffected by cerivastatin. Plasma concentration of cerivastatin and its metabolites increased 3- to 5-fold with no change in its elimination. No cerivastatin accumulation occurred with multiple dosing.

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 February 6, 2001).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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-006." 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 Professional" 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, call Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-740/S006

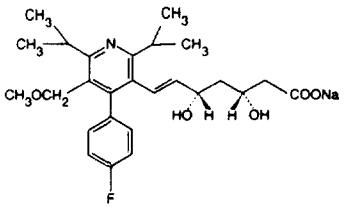
FINAL PRINTED LABELING

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, 0.3, 0.4 or 0.8 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.

Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including VLDL, IDL and remnants, can also promote atherosclerosis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association with nonlipid metabolic risk factors for coronary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Furthermore, the independent effect of raising HDL or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

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 VLDL-C and plasma triglycerides and increases plasma HDL-C and apolipoprotein A-1. 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 0.2 to 0.8-mg daily. In male and female patients at steady-state, the mean maximum concentrations (C_{max}) following evening cerivastatin tablet doses of 0.2, 0.3, 0.4, and 0.8-mg are 2.8, 5.1, 6.2, and 12.7 µg/L, respectively. AUC values are also dose–proportional over this dose range and the mean time to maximum concentration (t_{max}) is approximately 2 hours for all dose strengths. Following oral administration, the terminal elimination half-life ($t_{1/2}$) for cerivastatin is 2 to 4 hours. Steady-state plasma concentrations show no evidence of cerivastatin accumulation following administration of up to 0.8 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 comparable to, but do not exceed, the potency of the parent compound. Following a 0.8-mg dose of cerivastatin to male and female patients, mean steady state C_{max} values for cerivastatin, M1, and M23 were 12.7, 0.55, and 1.4 µg/L, respectively. Therefore, the cholesterol-lowering effect is due primarily to the parent compound, cerivastatin.

In vitro studies show that the hepatic cytochrome P450 (CYP) enzyme system catalyzes the cerivastatin biotransformation reactions. Specifically, two P450 enzyme sub-classes are involved. The first is CYP 2C8, which leads predominately to the major active metabolite, M23, and to a lesser extent, the other active metabolite, M1. The second is CYP 3A4, which primarily contributes to the formation of the less abundant metabolite, M1. The CYP 3A4 enzyme sub-class is also involved in the metabolism of a significant number of common drugs. The effect of the dual pathways of hepatic metabolism for cerivastatin is shown in clinical studies examining the effect of the known potent CYP 3A4 inhibitors, erythromycin and itraconazole. In these interaction studies, specific inhibition of the CYP 3A4 enzyme sub-class resulted in a 1.4- to 1.5-fold mean increase in cerivastatin plasma levels following co-treatment with erythromycin or itraconazole, possibly because of metabolism via the alternate CYP 2C8 pathway.

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} $\leq$ 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-C, LDL-C, VLDL-C, apo B, and TG and increasing HDL-C and apo A1 in patients with heterozygous familial and non-familial forms of hypercholesterolemia and in mixed dyslipidemia. Over 5,000 patients with Type IIa and IIb hypercholesterolemia were treated in trials of 4 to 104 weeks duration.

The effectiveness of BAYCOL® in lowering plasma cholesterol has been shown in men and women, in patients with and without elevated triglycerides, and in the elderly. In four large, multicenter, placebo-controlled dose response studies in patients with primary hypercholesterolemia, BAYCOL® given as a single daily dose over 8 weeks, significantly reduced Total-C, LDL-C, apo B, TG, total cholesterol/HDL cholesterol (Total-C/HDL-C) ratio and LDL cholesterol/HDL cholesterol (LDL-C/HDL-C) ratio. Significant increases in HDL-C were also observed. The median (25th and 75th percentile) percent changes from baseline in HDL-C for Baycol 0.2, 0.3, 0.4, and 0.8 mg were +8 (+1, +15), +8 (+1, +14), +7 (0, +14), and +9 (+2, +16), respectively. 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. (Pooled results at week 8 are presented in Table 1).

Table 1
Response in Patients with Primary Hypercholesterolemia
Mean Percent Change from Baseline to Week 8
Intent-To-Treat Population

Dosage	N[1]	Total-C	LDL-C	Apo-B	TG[2]	HDL-C	LDL-C/ HDL-C	Total-C/ HDL-C
Placebo	608-620	+1	0	+1	0	+2	-1	0
BAYCOL® qd								
0.2 mg	150-151	-18	-25	-19	-16	+9	-31	-24
0.3 mg	494-497	-22	-31	-24	-16	+8	-35	-27
0.4 mg	754-758	-24	-34	-27	-16	+7	-38	-29
0.8 mg	731-735	-30	-42	-33	-22	+9	-46	-35

1 - N given as a range since test results for each lipid variable were not available in every patient
2 - Median percent change from baseline

In a pool of eight studies in patients with hypercholesterolemia and TG levels ranging from 250 mg/dL to 500 mg/dL who were treated for at least eight weeks, the following reductions in TG and increases in HDL-C were observed at Week 8 as shown in Table 2 below:

Table 2
Median Percent Change from Baseline to Week 8
in Patients with Baseline TG between 250-500 mg/dL

	Placebo	BAYCOL® 0.2 mg	BAYCOL® 0.3 mg	BAYCOL® 0.4 mg	BAYCOL® 0.8 mg
N[1]	135-138	127-129	156-157	139	125
Triglycerides	-3.3	-22.6	-22.4	-26.2	-30.7
HDL-C	3.1	7.3	9.2	10.7	13.3

1 - N given as a range since test results for each lipid variable were not available in every patient

In a large clinical study, the number of patients meeting their National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP) II target LDL-C levels on BAYCOL® 0.4 and 0.8 mg daily was assessed. The results up to 24 weeks are shown in Table 3 below:

Table 3
Percent of Patients Reaching NCEP-ATP II Goal
Up to 24 Weeks of Treatment with BAYCOL® 0.4 mg and 0.8 mg

NCEP-ATP II Treatment Guidelines			Patients Reaching LDL-C Target Up to 24 Weeks			
Risk Factors for CHD	Baseline LDL-C (mg/dL)	Target LDL-C (mg/dL)	BAYCOL® 0.4 mg		BAYCOL® 0.8 mg	
			Baseline LDL-C Mean (mg/dL)	Percent To Goal	Baseline LDL-C Mean (mg/dL)	Percent To Goal
< 2 risk factors	≥190	< 160	234 (n=33)	79%	224 (n=156)	79%
≥ 2 risk factors	≥ 160	< 130	204 (n=43)	65%	201 (n=186)	72%
CHD	≥ 130	≤ 100	188 (n=34)	24%	187 (n=99)	53%

INDICATIONS AND USAGE

BAYCOL® (cerivastatin sodium tablets) is indicated as an adjunct to diet to reduce elevated Total-C, LDL-C, apo B, and TG and to increase HDL-C 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. 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.

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 of 400 mg/dL or less, 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 4.

Table 4
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**).

Concurrent treatment with gemfibrozil due to a risk for rhabdomyolysis (see WARNINGS: Skeletal Muscle).

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, regardless of baseline status) have been reported in 0.5% of patients treated with cerivastatin sodium in the US over an average period of 11 months. The incidence of these abnormalities was 0.1%, 0.4%, 0.9% and 0.6% for BAYCOL® 0.2, 0.3, 0.4, and 0.8 mg respectively. These abnormalities usually occurred within the first 6 months of treatment, usually 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: **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 seen in 0.4% of patients in U.S. cerivastatin clinical trials. In one clinical study using BAYCOL 0.8 mg as the starting dose, women over 65 years of age, especially those with low body weight, were observed to be at an increased risk of myopathy. 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.

The combined use of HMG-CoA inhibitors and fibrates generally should be avoided. The use of fibrates alone may be associated with myopathy including rhabdomyolysis and associated renal failure. **The combined use of cerivastatin and gemfibrozil is contraindicated due to a risk for rhabdomyolysis (see Contraindications).**

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.

ITRACONAZOLE: In hypercholesterolemic patients, following a 0.3 mg dose of cerivastatin, steady-state cerivastatin AUC and C_{max} increased 38% and 12%, respectively after 10 days with co-administration of 200 mg itraconazole, a potent inhibitor of cytochrome P450 3A4. Cerivastatin half-life was approximately 5 hours (a 64% increase) following co-administration with itraconazole, which would not lead to accumulation of cerivastatin upon multiple dosing. The administration of 0.3 mg of cerivastatin concomitantly with itraconazole has no effect on itraconazole pharmacokinetics.

In a single dose crossover study using 0.8 mg cerivastatin, the AUC and C_{max} of cerivastatin were increased 27% and 25% respectively during concomitant itraconazole treatment.

OMEPRAZOLE: There were no changes in the pharmacokinetic parameters of either cerivastatin or its major active metabolites, or of omeprazole in healthy young males given single 0.3 mg oral doses of cerivastatin alone or on the fifth day of a five-day omeprazole 20 mg daily pre-treatment.

GEMFIBROZIL: The potential for clinically relevant interaction between gemfibrozil and cerivastatin has not been assessed in clinical trials. However, during postmarketing surveillance, patients on cerivastatin who experienced rhabdomyolysis and associated renal failure, were in most cases also taking gemfibrozil. (See **CONTRAINDICATIONS** and **WARNINGS: Skeletal Muscle).**

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.

CYCLOSPORINE: The single dose pharmacokinetics of 0.2 mg of cerivastatin in healthy subjects was compared to the pharmacokinetics of single and multiple doses in renal transplant patients who were at steady-state with respect to cyclosporine. Cyclosporine levels were unaffected by cerivastatin. Plasma concentrations of cerivastatin and its metabolites increased 3- to 5-fold with no change in its elimination. No cerivastatin accumulation occurred with multiple dosing.

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}, measured as free drug), that were about 17 times higher than the mean values in humans taking 0.8 mg/day. No CNS lesions were observed after chronic treatment with cerivastatin for up to two years in the mouse (up to 6 times human $C_{max\ free}$ drug levels) and rat (in the range of human $C_{max\ free}$ drug levels).

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 2-year study was conducted in rats with dietary administration resulting in average daily doses of cerivastatin of 0.007, 0.034, or 0.158 mg/kg. The high dosage level corresponded to plasma free drug levels (AUC) of approximately 2 times those in humans following a 0.8-mg oral dose. Tumor incidences of treated rats were comparable to controls in all treatment groups. In a 2-year carcinogenicity study conducted in mice with dietary administration resulting in 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 $\geq$ 9.1 mg/kg (AUC_{free} values about 3 times human at 0.8 mg/day). Hepatocellular carcinomas were significantly increased in male mice at $\geq$ 1.8 mg/k (AUC_{free} values in the range of human exposure at 0.8 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 (in the range of human $C_{max\ free}$ drug levels). At a dose of 0.3 mg/kg/day (about 3 times human $C_{max\ free}$ drug levels), 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 (in the range of human $C_{max\ free}$ drug levels), 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 17-fold the human exposure at doses of 0.8 mg based on $C_{max\ free}$), 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 about 6 times the human exposure ($C_{max\ free}$) for rats and 3 times the human exposure for rabbits ($C_{max\ free}$) at a human dose of 0.8 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. In one clinical study using BAYCOL 0.8 mg as the starting dose, women over 65 years of age, especially those with low body weight, were observed to be at an increased risk of myopathy. Caution should be exercised when titrating such patients to the 0.8 mg dose of BAYCOL.

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

Cerivastatin sodium has been evaluated for adverse events in more than 5,000 patients worldwide. In the U.S. placebo-controlled clinical studies, discontinuations due to adverse events occurred in 3.1% of cerivastatin sodium treated patients and in 2.0% of patients treated with placebo. Adverse reactions have usually been mild and transient.

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 Table 5 below:

Table 5
Adverse Experiences occurring in ≥2% Patients in U.S. Placebo Controlled Clinical Studies

Adverse Event	BAYCOL® (n = 2231)	Placebo (n = 702)
Any event	63.2%	63.0%
Pharyngitis	9.6%	12.1%
Headache	8.5%	9.5%
Rhinitis	8.3%	10.1%
Sinusitis	4.7%	5.0%
Accidental injury	4.4%	5.6%
Arthralgia	4.3%	3.4%
Dyspepsia	3.8%	4.8%
Flu syndrome	3.7%	6.3%
Back pain	3.4%	5.0%
Asthenia	3.4%	2.1%
Diarrhea	3.3%	3.3%
Rash	3.0%	4.4%
Myalgia	2.5%	2.3%
Abdominal pain	2.5%	3.0%
Nausea	2.4%	3.1%
Leg pain	2.2%	1.4%
Constipation	2.2%	2.0%
Dizziness	2.1%	2.4%
Flatulence	2.1%	2.7%
Chest pain	2.0%	1.8%
Bronchitis	1.3%	2.1%

The following effects have been reported with drugs in this class; not all effects listed below have necessarily been associated with cerivastatin therapy.

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 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, 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, creatine kinase, 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 generally associated with the use of BAYCOL®, a casual 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.

Body as a Whole: Asthenia, fever, headache, anorexia, abdominal pain, epistaxis, edema.

Cardiovascular System: Hypertension, angina pectoris.

Digestive System: Colitis, constipation, diarrhea, duodenal ulcer, dyspepsia, flatulance, gastrointestinal disorder, gastrointestinal hemorrhage, hepatitis, nausea.

Hemolytic and Lymphatic System: Anemia, leukopenia.

Hypersensitivity Reaction: Allergic reaction, anaphylactoid reaction, angioedema, urticaria.

Nervous System: Paralysis, somnolence.

Musculoskeletal System: Myalgia, myasthenia, myopathy, myositis, rhabdomyolysis, hypertonia, hyperkinesia.

Respiratory System: Cough increase.

Urogenital System: Acute renal failure secondary to myoglobinuria.

Special Senses: Cataract specified, visual disturbance, blurred vision.

Laboratory Abnormalities: Amylase increase, elevated transaminases, laboratory tests abnormal, kidney function abnormal, creatine phosphokinase increase.

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**). Concurrent treatment with gemfibrozil is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS: Skeletal Muscle**).

OVERDOSAGE

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 starting-dose of BAYCOL® is 0.4 mg once daily in the evening. The dosage range is 0.2 mg to 0.8 mg. Cerivastatin sodium may be taken with or without food. In patients with significant renal impairment (creatinine clearance ≤60 mL/min/1.73m^2) the lower doses are recommended.

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

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 or 0.3 mg is recommended (see **CLINICAL PHARMACOLOGY - Special Populations - Renal**).

HOW SUPPLIED

BAYCOL® (cerivastatin sodium tablets) is supplied as 0.2-mg, 0.3-mg, 0.4-mg and 0.8-mg tablets. The different tablet strengths can be identified as follows:

		Markings	
Strength	**Color**	**Front**	**Back**
0.2 mg	light yellow	283	200 MCG
0.3 mg	yellow brown	284	300 MCG
0.4 mg	ocher	285	400 MCG
0.8 mg	brown orange	286	800 MCG

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

Bottles of 30:	0.4 mg	(NDC 0026-2885-69)
	0.8 mg	(NDC 0026-2886-69)
Bottles of 90:	0.2 mg	(NDC 0026-2883-86)
	0.3 mg	(NDC 0026-2884-86)
	0.4 mg	(NDC 0026-2885-86)
	0.8 mg	(NDC 0026-2886-86)

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

References:

[1] **Classification of Hyperlipoproteinemias**

		Lipid Elevations	
Type	**Lipoproteins Elevated**	**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

Rx Only

APPEARS THIS WAY
ON ORIGINAL

Patient Information About:

BAYCOL®

(cerivastatin sodium tablets)

Read this information carefully before you start taking your medicine. Read the information you get with your medicine each time you refill your prescription. There may be new information. This information does not take the place of talking with your doctor.

What is Baycol®?

Baycol [BAY-call] is a prescription medicine that reduces the total amount of cholesterol that your body makes. It also lowers the level of your LDL (bad) cholesterol. Baycol is used by adults with high cholesterol, when diet and exercise have not lowered cholesterol enough. You should follow a diet low in fat and cholesterol and exercise regularly when taking Baycol.

Who should not take Baycol?

Do not take Baycol if you

- Take Lopid (gemfibrozil).
- Take certain other medicines. Tell your doctor about other medicines and supplements. You can get serious muscle problems that can lead to kidney failure if you take Baycol with some medicines. One of these medicines is Lopid (gemfibrozil).
- Are pregnant or breast feeding or if you may become pregnant. Baycol may harm the baby.
- Have liver disease or possible liver problems.

Tell your doctor if you had liver problems in the past or if you drink a lot of alcohol (three (3) or more drinks per day). Your doctor may want to start you on the lower doses of Baycol and check you more often.

Tell your doctor if you will have major surgery, have been badly injured, have epilepsy, problems with your hormones or serious kidney problems. You may need to stop taking Baycol for a while.

Children should not take Baycol.

How should I take Baycol?

Take Baycol once a day in the evening, at about the same time each day. Swallow it whole with liquid. You can take it with or without food.

If you miss your daily dose, do not take two doses the next day. Rather, skip the dose and go back to your regular schedule on the next day. Do not take 2 doses at one time.

Continue with your diet and exercise program while taking Baycol.

Your doctor may do blood tests to check for liver problems before you start taking Baycol, at 6 and 12 weeks after you start taking it, and then every 6 months. Your blood should also be checked if your dose is increased.

What should I avoid while taking Baycol?

Do not

- Take Lopid (gemfibrozil)
- Breast feed since Baycol can pass through the milk and may harm the baby.
- Take Baycol while you are pregnant. If you become pregnant while taking Baycol, stop taking it and tell your doctor right away.
- Take certain other medicines. Ask your doctor what medicines you should not take.

What are the possible side effects of Baycol?

The most common complaints from patients taking Baycol are headache, sore throat, runny nose, stuffy nose, joint and muscle pain, diarrhea, and rash. If you develop these or other symptoms that you think may be caused by Baycol, contact your doctor.

Muscle and kidney problems. If you experience any unexplained muscle pain, tenderness, or weakness at any time during treatment with Baycol, you should notify your doctor immediately. Rarely, there is a risk of muscle breakdown resulting in kidney damage. The risk of this breakdown is greater in patients taking certain other drugs along with Baycol such as Lopid® (gemfibrozil) as well as cyclosporine, fibric acid derivatives, erythromycin, azole antifungals or lipid-lowering doses of niacin. If you are uncertain whether you are taking one of these medications, speak with your doctor. Because of these risks, your doctor should carefully monitor you for any muscle pain, tenderness or weakness, particularly during the initial months of treatment, if the dose of Baycol is increased, or if you are a woman over 65 years of age.

Tell your doctor right away if you get unexpected muscle pain, tenderness or weakness, especially if you also have a fever or feel sick. These may be sign of a serious side effect.

Liver problems Some patients taking Baycol have blood tests that show possible liver problems. Your doctor will check your liver function with blood tests.

General advice about prescription medicines
Medicines are sometimes prescribed for conditions that are not described in patient information leaflets. This medicine is for your use only. Never give it to other people. Do not use Baycol for a condition for which it was not prescribed. Ask your doctor if you have any questions. You can ask your doctor or pharmacist for information about Baycol that was written for health care professionals.

This information does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment. See your health care professional for full prescribing information.

Bayer Corporation
Pharmaceutical Division
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Rx Only

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-740/S006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-740 (SLR-006)	SUBMISSION DATE: 08-03-1999
BRAND NAME:	Baycol®
GENERIC NAME:	Cerivastatin
REVIEWER:	Xiaoxiong (Jim) Wei, M.D., Ph.D.
SPONSOR:	Bayer, West Haven, CT
TYPE OF SUBMISSION:	Supplemental NDA (Labeling change)

SYNOPSIS

On August 03, 1999, Bayer submitted a supplement to NDA20-740 for labeling changes for drug metabolism and drug interactions. The sponsor submitted in vitro studies using human liver microsomes, CYP cDNA expressed cell lines, and in vivo cerivastatin interaction studies with potent inhibitory drugs itraconazole and erythromycin. These in vitro and in vivo studies indicate that there are dual metabolic pathways of cerivastatin and M1 is mediated by both CYP3A4 and CYP2C8, and M23 is mediated mainly by CYP2C8 and there is no CYP3A4 involvement in the formation of M23. The concurrent administration of Itraconazole 200 mg qd or erythromycin 500 mg bid for 10 days increased the steady state AUC of cerivastatin (0.3 mg qd) by 38% and 50%, respectively.

[redacted] Like other statins, cyclosporin greatly increased the cerivastatin exposure by 3 to 5 fold in renal transplant patients compared to healthy subjects.

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CLINICAL PHARMACOLOGY/DRUG METABOLISM

1. What are the metabolic pathways of cerivastatin?

The sponsor conducted a series of in vitro studies to determine the metabolic pathways of cerivastatin and CYP isozymes involved. The sponsor also performed in vivo drug interaction studies with CYP3A4 inhibitors, itraconozole and erythromycin to further confirm the findings from in vitro studies.

In human microsomes cerivastatin is subject to two primary biotransformation reactions: Demethylation of the benzylic methylther leads to metabolite M-1, whereas hydroxylation of one methyl group in the 6'-isopropyl moiety furnishes metabolite M-23.

The sponsor conducted an in vitro metabolism study with CYP cDNA expressed cell lines including CYP3A4 and CYP2C8. The results showed that both CYP3A4 and CYP2C8 could form metabolites M1. But there was no formation of metabolite M23 in the CYP3A4 expressed cell line.

In the inhibition experiments, the selective Cyp3A4 inhibitor TAO (triacetylcandomycin) was used in a concentration at 5 μM. Cerivastatin metabolism was reduced by TAO to about 60% of control and the formation of metabolites M-1 and M-23 was inhibited to similar extents over a 3-hours reaction period. Contrary to the CYP3A4 expressing cell line, TAO inhibition equally affected metabolic pathways, hydroxylation and demethylation.

Table 1. Inhibition of cerivastatin metabolism in human liver microsomes by coincubation with TAO (triacetylcandomycin).

Inhibition of cerivastatin metabolism in human liver microsomes by coincubation with TAO

Time	Incubation	Cerivastatin	M-1	M-23	M-24
		% of radioactivity			
Start	Control[a]	100	—	—	—
	TAO1[b]	100	—	—	—
	TAO2[c]	100	—	—	—
0.5 hr	Control	65.4	16.8	15.3	1.2
	TAO1	74.7	12.2	12.1	—
	TAO2	80.5	9.4	9.6	—
1 hr	Control	50.7	21.9	20.0	2.6
	TAO1	60.1	17.4	18.1	1.2
	TAO2	70.0	14.5	13.2	1.4
2 hr	Control	30.5	29.2	26.4	6.9
	TAO1	44.6	23.3	25.3	3.4
	TAO2	53.4	20.6	20.1	2.3
3 hr	Control	17.7	33.4	30.0	11.7
	TAO1	29.7	28.1	30.3	5.7
	TAO2	44.7	24.4	24.7	3.6

[a] No inhibitor was added.
[b] TAO and drug were added simultaneously.
[c] The drug was added after 20 min preincubation with TAO.

The sponsor further conducted in vivo multiple-dose drug interaction studies to evaluate the effect of 10 days concurrent treatment of itraconazole 200 mg qd on the pharmacokinetics of cerivastatin 0.3 mg qd. Steady–state cerivastatin pharmacokinetic profile was determined on Day 5 (the day before itraconazole given) and Day 15. The results indicated that the AUC and T1/2 of parent drug, cerivastatin increased by 38% and 64%, respectively, and the AUC and T1/2 for M23 increased by 50% and 77%, respectively. However, AUC, Cmax and T1/2 for M1 were not altered significantly (decrease by 4% - 12%). A comparison of the mean pharmacokinetic parameters was listed in the following table:

Table 2.

Parameter	Cerivastatin alone	Cerivastatin + Itraconazole	Ratio of Means (N=16, 5, 7)
Cerivastatin			
AUC	23.8	32.9	1.38
Cmax	4.8	5.6	1.15
T1/2	3.4	5.5	1.64
Metabolite M 1			
AUC	1.73	1.64	0.95
Cmax	0.22	0.19	0.86

T1/2	5.4	5.1	0.96
Metabolite M 23			
AUC	5.58	8.41	1.5
Cmax	0.58	0.76	1.31
T1/2	4.94	8.72	1.77

Another in vivo multiple-dose drug interaction study was to evaluate the effect of 10 days concurrent treatment of erythromycin 500 mg bid on the pharmacokinetics of cerivastatin 0.3 mg. Steady –state cerivastatin pharmacokinetics were measured on Day 5 (the day before erythromycin given) and Day 15. The AUC of parent drug, cerivastatin increased by 51%. Cmax for M23 increased by 28%. However, Cmax for M1 was not altered significantly (decrease by 10%). A comparison of the mean pharmacokinetic parameters was listed in the following table:

Table 3.

Parameter	Cerivastatin alone	Cerivastatin + Erythromycin	Ratio of Means (N=13)
Cerivastatin			
AUC	23.6	35.5	1.51
Cmax	3.7	4.6	1.24
T1/2	3.5	4.9	1.41
Metabolite M 1			
Cmax	0.30	0.27	0.90
Metabolite M 23			
Cmax	0.57	0.73	1.28

Based on the these in vitro and in vivo studies, the sponsor summarized schematically the metabolic pathways of cerivastatin as follows:

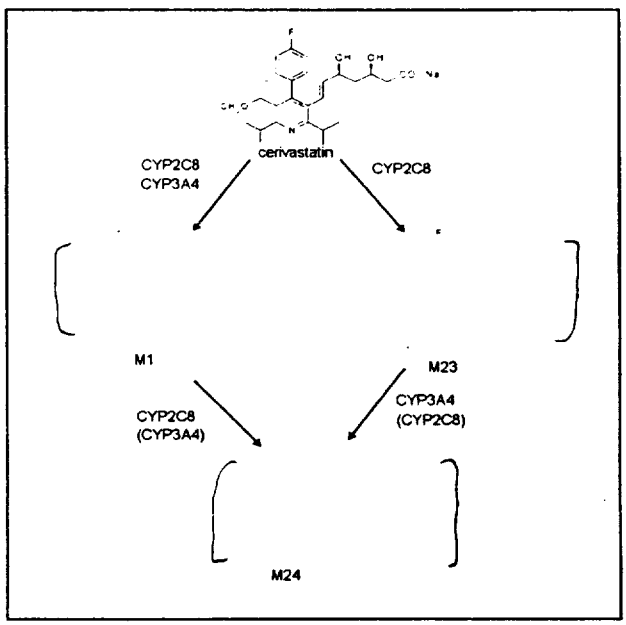


Figure 1. Metabolic pathways of cerivastatin

Reviewer's comment:

Based on the facts (1) there was no formation of metabolite M23 from the incubation with the cDNA expressed CYP3A4, (2) in vivo studies with potent CYP3A4 inhibitors showed that the metabolism of parent drug and M23 was inhibited and there was no change in the formation of metabolite M1. This

reviewer agrees with the sponsor that the dual metabolic pathways of cerivastatin allowed attenuation of the CYP3A4 inhibition on the M1 pathway, by shifting to M23 pathway (increase in M23 AUC by 50%). This reviewer also agrees with the sponsor that the formation of M23 is not mediated by CYP3A4 based on these key findings although the results from the TAO incubation study showed that TAO inhibited both metabolic pathways (Figure 1).

3. Are there no drug interactions between cerivastatin and omeprazole as we anticipated?

The sponsor performed in vivo drug interaction study between cerivastatin and omeprazole. Twelve male subjects received single oral dose of 0.3 mg cerivastatin alone or on the fifth day of five days omeprazole 20 mg qd pretreatment. No pharmacokinetic interaction was noted for either cerivastatin or its major metabolites. The pharmacokinetics of omeprazole was also unchanged. The following table describes the results of major pharmacokinetic parameters of cerivastatin.

Parameter	Units	BAY w 6228 in combination with omeprazole	BAY w 6228 alone
AUC	µg*h/L	14.0 / 1.55	13.9 / 1.53
AUC_{norm}	kg*h/L	3.61 / 1.57	3.59 / 1.52
C_{max}	µg/L	2.44 / 1.59	2.53 / 1.61
$C_{max,norm}$	kg/L	0.63 / 1.61	0.65 / 1.61
t_{max} +	h	1.5	2.5
$t_{1/2}$	h	2.5 / 1.21	2.3 / 1.25

+ median (range)

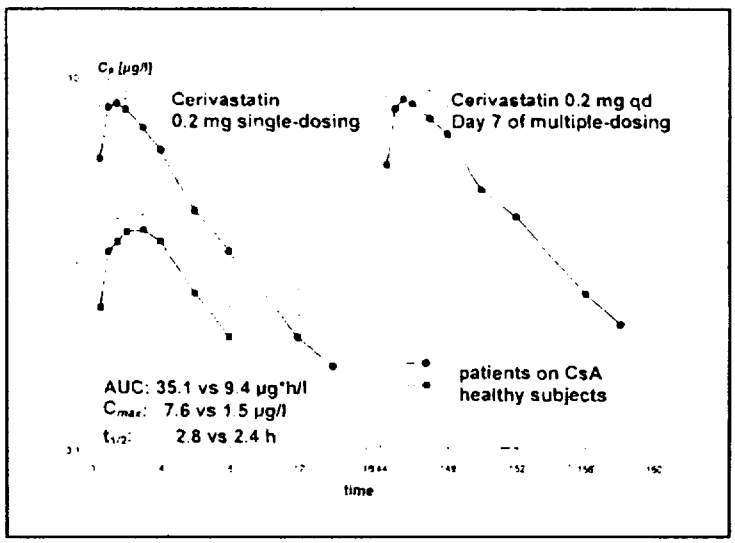
Reviewer's comment:

Omeprazole is mainly metabolized by CYP2C19. Therefore, this reviewer agrees with the sponsor the negative drug interaction is anticipated.

4. Does cyclosporin dramatically increase the bioavailability of cerivastatin like other statins?

Co-administration of cerivastatin 0.2 mg qd to twelve kidney transplant patients treated with individual doses of cyclosporin A resulted in a 3-5 fold increase in plasma concentrations of cerivastatin and its metabolites when compared to the healthy control group. Cerivastatin elimination was unaffected and no significant accumulation under multiple dosing condition. Cerivastatin had no influence on the steady state whole blood concentration/time profiles of cyclosporin or cyclosporin plus metabolites in these patients. The following figure shows that the difference of pharmacokinetics of cerivastatin with and without cyclosporin A:

Figure 3. Cerivastatin plasma Concentration-time profiles in healthy subjects and renal Transplant patients.



Reviewer's comment:
Apparently, cyclosporin inhibited the efflux pump in the intestines, therefore increased the bioavailability. Because T1/2 was not altered, cyclosporin is unlikely to inhibit the metabolism of cerivastatin. Plasma levels of cyclosporin were not changed by concurrent treatment of cerivastatin.

LABELING COMMENTS:
(~~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)

Precautions / Drug Interactions

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RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed supplemental NDA 20-740 (drug metabolism and drug interactions) submitted on August 03, 1999. The proposed labeling changes are acceptable except [redacted] This recommendation and labeling comment should be sent to the sponsor as appropriate.

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

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RD/FT initialed by Hae-Young Ahn, Ph.D., Team Leader

CC: NDA 20-740 (orig., 1 copy), HFD-510 (Simoneau), HFD-850 (Lesko, Huang), HFD-870 (Wei, Ahn, Malinowski), CDR.

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Labeling

Appendix 2. Study reports

2. Study synopsis

Title of the study:	A Study to Evaluate the Potential Reciprocal Interaction Between Cerivastatin and Itraconazole in Hypercholesterolemic Patients
Investigator(s):	[redacted]
Study center(s):	[redacted]
Publications (references):	No publications available
Period of study:	May 9, 1997 to July 25, 1997 (First patient enrolled - Last patient's observation)
Clinical phase:	Phase I
Objectives:	The primary objective of this study was to evaluate a potential reciprocal cerivastatin/itraconazole drug-drug interaction by comparing the steady-state pharmacokinetics of cerivastatin with and without concurrent dosing of itraconazole. The secondary objective was an evaluation of the effect of cerivastatin on the single-dose pharmacokinetics of itraconazole
Methodology (design of study):	This study was designed as a single-center, non-randomized, non-blinded, multiple-dose drug interaction study evaluating the effect of 10 days concurrent itraconazole 200 mg daily on the pharmacokinetics of cerivastatin 0.3 mg daily. The single-dose pharmacokinetics of itraconazole were also evaluated alone and with concurrent treatment with cerivastatin Patients were screened by physical examination including funduscopy, vital signs, electrocardiogram (ECG) and laboratory testing On Day -9 patients were given a single oral dose of itraconazole 200 mg. Patients were confined to the clinic overnight and had blood samples drawn for a 24-hour itraconazole pharmacokinetic profile. Nine days later on Day 1 patients began cerivastatin 0.3 mg once each evening. On the evening of Day 5, patients entered the clinic to begin a 2½-day confinement. Blood samples were drawn for a 24-hour cerivastatin pharmacokinetic profile on the evening of Day 5. On the evening of Day 6, patients began daily itraconazole dosing (200 mg) concurrent with the cerivastatin dosing. Patients were discharged from the clinic on the evening of Day 7. The dosing combination continued for a total of 10 days with the final doses of cerivastatin and itraconazole administered on the evening of Day 15. Patients returned to the clinic on Day 15 to have blood samples drawn for a 24-hour cerivastatin pharmacokinetic profile

Methodology (design of study):	An end of study physical examination, ECG and clinical laboratory tests were conducted on the morning of Day 16; patients were discharged from the clinic on that evening after the final pharmacokinetic blood draw was completed. Safety parameters, including adverse events, vital signs, ECGs, clinical laboratory tests, and physical examinations were monitored throughout the study.
Number of patients:	In total, 19 patients with primary hypercholesterolemia were enrolled and received at least one dose of cerivastatin in Study D97-011 including 6 males and 13 females. Age ranged from 43 to 64 years. All 19 patients were valid for safety analysis. Three patients who were discontinued from treatment for administrative reasons were excluded from the pharmacokinetic evaluations.
Diagnosis and main criteria for inclusion:	Male or female patients between the ages of 25 to 65 years inclusive with primary hypercholesterolemia, i.e., calculated LDL-cholesterol $\geq$ 130 mg/dL were selected for enrollment.
Test product, dose and mode of administration, batch number:	Cerivastatin 0.3 mg tablets given once each evening between 5 and 6 p.m. with dinner from Day 1 to Day 15. The batch number of cerivastatin used in this study was 532005D. Itraconazole (Sporanox®) 200 mg given as two 100 mg capsules once each evening between 5 and 6 p.m. with dinner. A single-dose was administered on Day -9, daily doses were administered from Day 6 to Day 15 concurrently with cerivastatin. The batch number of itraconazole used in this study was 96N415E
Duration of treatment:	Each patient participated in the trial for approximately 25 days. Patients were confined to the clinic for a total of 4 overnight stays. Patients who completed the entire study received a total of 15 doses of cerivastatin 0.3 mg and a total of 11 doses of itraconazole 200 mg.
Reference therapy, dose and mode of administration, batch number:	No reference therapy was employed in this study.
Criteria of evaluation:	Pharmcokinetics: comparison of steady-state cerivastatin pharmacokinetic parameters AUC_{0-24}, C_{max}, t_{max} and $t_{1/2}$ on Day 5 (alone) and on Day 15 (in combination with itraconazole). The secondary objective was the comparison of single-dose itraconazole parameters AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, t_{max} and t_{max} and $t_{1/2}$ on Day -9 (alone) and on Day 6 (in combination with cerivastatin).
Criteria of evaluation:	Safety: examination of the incidence of adverse events and laboratory abnormalities, as well as changes in vital signs, physical examination results including funduscopy and ECGs.

Statistical methods: Summary statistics were presented for demographic, vital signs, ECG and pharmacokinetic variables. Frequencies of adverse events were presented by treatment. Listings were presented for adverse events and all laboratory data.

For all pharmacokinetic parameters, logarithmically (natural log) transformed estimates for each patient were analyzed using two-way analysis of variance (ANOVA) with terms for day and patient. Log-scale least square means and log-scale differences were exponentiated to obtain geometric least squares means and ratio estimates. Lower and upper limits based on 90% confidence intervals are presented, as are significance levels at which 80% equivalence from below and 125% equivalence from above could be claimed. The overall significance level for two-sided equivalence is the maximum of these two p-values. Pairwise two-sided tests for treatment inequality were also conducted.

Summary and conclusions:

Summary of pharmacokinetics:
The primary analysis was the comparison of the steady-state pharmacokinetics of cerivastatin with and without concurrent dosing of itraconazole, Day 15 and Day 5, respectively.

Cerivastatin Pharmacokinetics: Geometric Mean (CV%), n=16

Parameter	Cerivastatin Alone	Cerivastatin+ Itraconazole	Ratio of Means	90% CI about the Ratio
AUC_{0-24} (µg•h/L)	23.8 (41%)	32.9 (35%)*	1.38	(1.245, 1.538)
Cmax (µg/L)	4.8 (44%)	5.6 (48%)	1.15	(0.957, 1.387)
$t_{½}$ (hr)	3.4 (31%)	5.5 (21%)*	1.64	(1.426, 1.878)

*Significantly different from cerivastatin alone at the 5% level.

Comparison of Day 15 (with itraconazole) to Day 5 (alone) cerivastatin pharmacokinetic variables revealed statistically significant increases in mean cerivastatin AUC_{0-24} and the mean elimination half-life ($t_{½}$). Steady-state cerivastatin AUC_{0-24} was increased 38% during concurrent itraconazole administration and $t_{½}$ was increased 64%. The observed 15% increase in C_{max} was not statistically significant; time to maximum concentration (t_{max}) was unchanged.

Pharmacokinetic variables for the cerivastatin metabolites BAY w 5679 (M1) and BAY 17-5111 (M23) are shown below.

Metabolite M1 Pharmacokinetics: Geometric Mean (CV%), n = 5 (n=6 for C_{max})

Parameter	Cerivastatin Alone	Cerivastatin+ Itraconazole	Ratio of Means
AUC_{0-24} (µg•h/L)	1.73 (34%)	1.64 (22%)	0.95
Cmax (µg/L)	0.22 (24%)	0.19 (24%)	0.86
$t_{½}$ (hr)	5.4 (69%)	5.1 (50%)	0.94

Metabolite M23 Pharmacokinetics: Geometric Mean (CV%), n=7 (n=8 for C_{max})

Parameter	Cerivastatin Alone	Cerivastatin+ Itraconazole	Ratio of Means
AUC_{0-24} (µg•h/L)	5.58 (23%)	8.41 (32%)	1.51
Cmax (µg/L)	0.58 (19%)	0.76 (44%)	1.31
$t_{½}$ (hr)	4.9 (24%)	8.7 (51%)	1.78

The mean AUC_{0-24} and C_{max} of metabolite M1 decreased 5% and 14%, respectively, during combination treatment of cerivastatin and itraconazole as compared to cerivastatin-only treatment. For the metabolite M23 mean AUC_{0-24} and C_{max} increased 51% and 31%, respectively, during combination treatment of cerivastatin and itraconazole as compared to cerivastatin-only treatment. Although these results are based on a small sample size they are consistent with expectations that inhibiting the CYP-3A4 enzyme (with itraconazole) would lead to a decrease in the metabolite (M1) formed by this enzyme sub-class and an increase in the metabolite (M23) that is not formed by this enzyme. This shifting of the metabolic fate of cerivastatin occurs as more parent compound is available to competing enzyme sub-class systems, in this case, CYP-2C8. This was also the same alteration of the metabolite pattern seen in a previous cerivastatin interaction study with another CYP-3A4 inhibitor, erythromycin.

An evaluation of the single-dose pharmacokinetics of itraconazole and with (Day 6) and without (Day -9) concurrent dosing of cerivastatin was also performed.

Itraconazole Pharmacokinetics: Geometric Mean (CV%), n=16

Parameter	Itraconazole Alone	Cerivastatin+ Itraconazole	Ratio of Means
AUC_{0-24} (µg•h/L)	1074.7 (63%)	1142.0 (59%)	1.06
Cmax (µg/L)	108.7 (70%)	118.7 (70%)	1.09
$t_{½}$ (hr)	12.0 (46%)	14.8 (48%)	1.23

2-OH Itraconazole Pharmacokinetics: Geometric Mean (CV%), n=16

Parameter	Itraconazole Alone	Cerivastatin+ Itraconazole	Ratio of Means
AUC_{0-24} (µg•h/L)	2756.6 (62%)	3292.2 (54%)	1.19
Cmax (µg/L)	199.9 (62%)	229.1 (49%)	1.15
$t_{½}$ (hr)	11.7 (50%)	13.4 (45%)	1.14

Itraconazole AUC_{0-24} was increased 6% and C_{max} was increased 9% during concurrent cerivastatin administration; these changes were not statistically significant. Changes in t_{max} and $t_{½}$ were small and were also not statistically significant. 2-OH Itraconazole AUC_{0-24} was increased 19% and C_{max} was increased 15% during concurrent cerivastatin administration; these changes also were not statistically significant. Changes in t_{max} and $t_{½}$ were again were small and not statistically significant.

Summary of safety:

A total of 12 (63.2%) of the 19 patients enrolled reported at least one treatment-emergent adverse event during the entire study; the most commonly reported event was headache occurring in 9 patients (47.4%). Most events were mild in intensity, generally of short duration and resolved without intervention other than analgesics. None of the events were classified as severe or serious and none of the patients discontinued the study due to adverse events.

Following the administration of a single dose of itraconazole, 10 (52.6%) of the 19 patients reported adverse events and during dosing with cerivastatin alone, 7 (36.8%) of the 19 patients reported at least one event. Of the 16 patients who received concurrent dosing of cerivastatin and itraconazole, 7 (43.8%) reported events. The most common adverse event reported during each dosing period was headache. None of the adverse events reported during the itraconazole alone or cerivastatin alone dosing periods were reported with a higher frequency during the concurrent dosing period.

There were no clinically significant changes in the hematology, clinical chemistry, and urinalysis parameters monitored during this study; no laboratory abnormalities were reported as adverse events. There were no clinically relevant changes in physical examination finding, vital signs, or on ECG.

Conclusion:

The results indicate that itraconazole, a known potent inhibitor of cytochrome P-450 3A4 has a relatively small and consistent effect on the study-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. Concurrent dosing of cerivastatin 0.3 mg qpm with itraconazole 200 mg qpm was well tolerated.

2. Study synopsis

Title of study:	A Study to Evaluate the Potential Reciprocal Interaction Between Cerivastatin and Erythromycin in Hypercholesterolemic Patients
Investigator(s):	[redacted]
Study center(s):	
Publications (references):	[redacted]
Period of Study:	July 30, 1996 to October 16, 1996
Clinical Phase:	I
Objectives:	The primary objective of this study was to compare the steady-state pharmacokinetics of cerivastatin with and without concurrent dosing of erythromycin. The secondary objective of the study was to evaluate the effect of cerivastatin on the single-dose pharmacokinetics of erythromycin.
Methodolgy:	Non-randomized, non-blinded, multiple-dose drug-drug interaction study evaluating the effect of 10 days concurrent erythromycin (ERY) 500 mg bid on the pharmacokinetics of cerivastatin (CER) 0.3 mg. The single-dose pharmacokinetics of ERY were also evaluated alone and with concurrent treatment with CER. Patients were first given a single oral dose of ERY on Day -9. Nine days later on Day 1 patients began CER 0.3 mg once each evening on an outpatient basis. Concurrent treatment with ERY 500 mg bid began on Day 6 and continued for 10 days. ERY single-dose pharmacokinetics were measured on Days -9 and 6. Steady-state CER pharmacokinetics were measured on Days 5 and 15. A comparison of the mean PK values for CER with and without concurrent ERY treatment was conducted. A secondary analysis of ERY plasma levels with and without concurrent CER treatment was also conducted. Safety parameters such as physical examination, ECG, funduscopy, and laboratory tests were monitored throughout the study. Adverse events were also recorded during the study.

Number of patients:	Sixteen patients with primary hypercholesterolemia were enrolled in this study. Nine patients were male and seven patients were female. Ages were from 50 to 74 years of age. All 16 patients completed the study and were valid for safety analysis. There were no drop-outs during the study. All sixteen patients enrolled completed the protocol. However, because of damage to the shipping container containing pharmacokinetic samples and disruption of sample labels, nearly all samples were lost for patient 1009. Of the remaining 15 patients, seven had one to six missing samples per profile. Samples for these seven patients were analyzed, and the resulting profiles were evaluated in a blinded fashion by the pharmacokineticist. Based on this blinded evaluation, patients 1010 and 1012 were declared invalid for pharmacokinetic evaluation because the number of concentration points available were not sufficient to generate pharmacokinetic parameters. Thus, three patients (1009, 1010, and 1012) were invalid for the cerivastatin pharmacokinetic analysis, and data from the remaining 13 patients were used in the pharmacokinetic analysis.
Diagnosis and main criteria for inclusion:	Primary hypercholesterolemia (calculated LDL-cholesterol ≥ 130 mg/dl)
Test product, dose and mode of administration, batch number:	Cerivastatin 0.3 mg tablet given once each evening between 7-9 pm, approximately 2 hours after dinner. Erythromycin 500 mg bid (as ERYC®, 2 x 250 mg delayed-release capsules manufactured by Parke-Davis) given at 7-9 am and 7-9 pm daily. Cerivastatin tablet batch number: 532005D; ERYC 250 mg capsule batch number: 90035D
Duration of treatment:	Cerivastatin 0.3 mg was dosed once each evening for 19 days (Days 1-19). Erythromycin 500 mg bid was dosed concurrently (evenings) with cerivastatin for 10 days (evening of Day 6 to the morning of Day 16)
Reference therapy, dose and mode of administration, batch number:	No reference therapy.
Criteria for evaluation:	Safety: Physical examination including funduscopy, vital signs, ECG, adverse events, and clinical laboratory laboratory. Pharmacokinetics: Primary objective was the comparison of steady-state cerivastatin parameters, AUC_{0-24}, C_{max}, t_{max} and $t_{1/2}$ on Day 5 (alone) and on Day 15 (with erythromycin). Secondary objective was the comparison of single-dose erythromycin parameters, AUC_{0-12}, C_{max}, t_{max} and $t_{1/2}$ on Day -9 (alone) and on Day 6 (with cerivastatin).
Statistical methods:	Summary statistics were presented for demographic, vital signs, ECG and pharmacokinetic variables. Listings were presented for adverse events and laboratory data. Analysis of variance was performed for cerivastatin pharmacokinetic variables.

Summary and conclusions:

Summary of Pharmacokinetics:
The primary analysis was the comparison of the steady-state pharmacokinetics of cerivastatin with and without concurrent dosing of erythromycin, Day 15 and Day 5, respectively.

Cerivastatin Pharmacokinetics (n = 13)

Parameter	Cerivastatin Alone (Day 5)	Cerivastatin + Erythromycin	Ratio of Means (CER+ERY/CER)	90 % C.I. About Ratio
AUC_{0-24} (µg*h/L)	23.6 (44%)	35 5 (44%)*	1.51	1.31 - 1.80
C_{max} (µg/L)	3.7 (63%)	4 6 (33%)	1.24	0.95 - 1.63
$t_{1/2}$ (hr)	3.5 (20%)	4.9 (30%)*	1.41	1.20 - 1.67

CER = cerivastatin; ERY = erythromycin * $p<0.05$

Cerivastatin AUC at steady state was increased 51% during concurrent erythromycin administration. The observed 24% increase in C_{max} was not statistically significant ($p > 0.1$) The mean elimination half-life was increased 41% The time to maximum concentration (t_{max}) was unchanged

An evaluation of the single-dose pharmacokinetics of erythromycin with (Day 6) and without (Day -9) concurrent dosing of cerivastatin was performed

Erythromycin Pharmacokinetics (n = 16)

Parameter	Erythromycin Alone	Erythromycin + Cerivastatin	Ratio of Means (ERY+CER/ERY)
C_{max} (µg/L)	0.97 (97.7%)	1.03 (92.8%)	1.06

The maximum concentration of erythromycin was unafffected by combined treatment with cerivastatin.

The levels of cerivastatin metabolites BAY w 5679 (M1) and BAY 17-5111 (M23) are shown below.

Metabolite M1 (n = 3)

Parameter	Cerivastatin Alone	Cerivastatin + Erythromycin	Ratio of Means (CER+ERY/CER)
C_{max} (µg/L)	0.30 (40%)	0.27 (36%)	0.9

Metabolite M23 (n = 5)

Parameter	Cerivastatin Alone	Cerivastatin + Erythromycin	Ratio of Means (CER+ERY/CER)
C_{max} (µg/L)	0.57 (66%)	0.73 (35%)	1.28

The maximum plasma concentration of metabolite M1 during combination treatment of cerivastatin and erythromycin decreased 10% compared to cerivastatin-only treatment. The maximum plasma concentration of metabolite M23 during combination treatment of cerivastatin and erythromycin increased 28% compared to cerivastatin-only treatment. These results are based on very small sample size, but are consistent with expectations that inhibiting CYP-3A4 enzyme would lead to a decrease in the metabolite (M1) which is formed by this enzyme sub-class, and an increase in the metabolite (M23) not formed by this enzyme sub-class. This shifting of the metabolic fate of cerivastatin occurs as more parent compound is available to competing enzyme sub-class systems, in this case, likely CYP-2C8. This was also the same alteration of the metabolite pattern seen in a previous single-dose cerivastatin - erythromycin interaction study.

Summary of safety:
Treatment-emergent adverse events were reported by 6 of 16 (38%) patients. One non-treatment-emergent adverse event, a mild arm bruise, was reported by patient 1012 two days before the study began (2 days prior to this patient's first dose of erythromycin). Of the 6 patients reporting treatment-emergent adverse events, 2 patients reported events starting during cerivastatin only treatment (Days 1-5 and 17-19), and 4 patients reported events starting during the combination of cerivastatin and erythromycin treatment (6-16). The most common event was headache (13%). The intensity of 5 adverse events was classified as mild, and 4 events were classified as moderate. There were no severe or serious adverse events reported. During the cerivastatin and erythromycin combination treatment phase of the study, one patient reported nausea and one patient reported diarrhea and sour stomach, these events were likely related to erythromycin which is known to cause gastrointestinal side effects.

There were no clinically significant changes in the hematology, clinical chemistry, and urinalysis parameters monitored during this study. There were minor transient elevations in the key chemistry parameters (transaminases, LDH, and CK) seen in four patients (all were less than 1 6 times the upper limit of normal). There were no significant changes detected on physical examination, vital signs, or electrocardiogram. There were no premature discontinuations from treatment for any reason.

Conclusions:
Administration of a 10-day treatment regimen of 500 mg bid erythromycin on a background of cerivastatin 0.3 mg qpm resulted in a statistically significant 51% increase in the mean cerivastatin AUC compared to the mean cerivastatin AUC without concurrent erythromycin. The mean cerivastatin C_{max} increased by 24%, but this change was not statistically significant. The increase in cerivastatin plasma concentration during combination treatment with erythromycin can be considered quite moderate in comparison to up to a 10-fold increase in lovastatin plasma levels seen when lovastatin is given in combination with erythromycin.

Concurrent dosing of cerivastatin 0.3 mg qpm with erythromycin 500 mg bid for 10 days was well tolerated. There were no changes on physical examination, vital signs or ECG. Adverse events were observed in 6 of 16 (38%) of the subjects; most were mild and short in duration. None of the events were classified as severe or serious. There were no premature discontinuations from treatment. Minor transient elevations in serum transaminase and CK values seen in four patients were not clinically significant, and in three of these cases, values returned to normal during continued treatment.

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2. Study synopsis

Title of the study:	Investigation of the influence of omeprazole on the pharmacokinetics of BAY w 6228 after single oral administration of 300 µg BAY w 6228 and a pretreatment phase with single administration of 20 mg omeprazole qd for five days in twelve healthy male volunteers in a randomised, non-blind crossover study (Study no. BAY w 6228/0177)
Investigator(s):	[redacted]
Study center(s):	[redacted]
Publications (references):	none
Period of study:	18 April to 05 May 1997
Clinical phase:	I
Objectives:	Primary objective of the study was to evaluate a possible influence of omeprazole on the pharmacokinetics of BAY w 6228.Secondary objectives of the study were the evaluation of safety and tolerability under concomitant administration of BAY w 6228 and omeprazole.
Methodology (design of study):	Single oral administration of 300 µg BAY w 6228 in one period together with 20 mg omeprazole after a pretreatment phase with 20 mg omeprazole qd for four days, in the other period after a washout-phase of one week without co-medication; randomised, non-blind, crossover comparison in healthy male subjects.
Number of patients:	Twelve healthy subjects were randomised. Twelve subjects were valid for the analysis of safety data. Twelve subjects were valid for the analysis of pharmacokinetic data.

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Diagnosis and main criteria for inclusion:	Healthy male subjects, aged between 18 to 45 years (mean ± SD: 31 ± 5 years; actual range: 22 - 40 years)
Test product, dose and mode of administration, batch number:	BAY w 6228 300 µg tablet; oral administration of one tablet in each period the volunteers were given the study medication in the morning on an empty stomach. The BAY w 6228 tables were swallowed together with 100 ml water of room temperatur. Batch no : 532 005D
Duration of treatment:	The study consisted of two periods with single oral administration of 300 µg BAY w 6228 in each period. In one of the two periods there was a co-medication with 20 mg omeprazole qd for five days.
Reference therapy, dose and mode of administration, batch number:	Omeprazole 20 mg capsule; oral administration of one capsule for five days in one period; on the four the profile day preceding days one tablet omeprazole was swallowed prior to the breakfast unchewed with a little bit of water. On the profile day it was swallowed on an empty stomach immediately after administration of BAY w 6228. Batch no.: 534 617K, packed with batch-no.: 532 005D
Criteria of evaluation:	Clinical observations physical examination, adverse events, vital signs, ECG, clinical chemistry, haematology, urinalysis Pharmacokinetic analysis: plasma concentrations of BAY w 6228 and metabolites M1 and M23, urine concentrations of metabolites M1 and M23; primary variables: AUC, AUC_{norm}, C_{max}, $C_{max,norm}$ secondary variables: $t_{1/2}$, MRT, t_{max}, only for the metabolites Ae_{ur}, Cl_{ren} plasma concentrations of omeprazole with variables AUC_{tau}, C_{max}, t_{max}, $t_{1/2}$

Statistical methods:	For all variables descriptive statistics including mean values, standard deviations (SD), minimum, median and maximum values (tables and graphs) were applied. Descriptive statistics for all pharmacokinetic variables including geometric mean values and standard deviations (SD); in addition, ANOVA to estimate the within-subject variation of AUC_{norm} and $C_{max,norm}$ for BAY w 6228 ; explorative 90% confidence intervals for the ratio combined dosing/mono-dosing The data processing and statistical analysis were performed in accordance with „Harmonization of data evaluation in pharmacokinetics", R-report 5747 (P), Bayer AG, 1992. Pharmacokinetic data of M1 and M23 were listed and described.

/s/

Xiao-xiong Wei
12/21/00 06:43:08 PM
BIOPHARMACEUTICS

Hae-Young Ahn
12/22/00 02:14:43 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-740/S006

CORRESPONDENCE

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: January 9, 2001

To: Frederich K. Sundermann	**From:** Margaret Simoneau
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Subject: NDA 20-740 (SLR-006) - Labeling change

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

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Labeling