VII. Pharmacokinetic/Pharmacodynamic Relationships

A Phase-IIa study was conducted to evaluate the safety and tolerability of 300 μg cerivastatin administered once daily for 28 days in patients with hypercholesterolemia using a placebo-controlled, double-blind, parallel group design. Pharmacokinetic profiles of cerivastatin were obtained from 23 subjects who received active drug. The results indicated that cerivastatin was absorbed quite rapidly, with a mean t_{max} of 2.1 hours [redacted] C_{max} averaged 3.9 μg/L elimination was characterized by a half-life of approximately 3 hours and AUC 24.6 was µg•h/l.

These pharmacokinetic data in the target patient population are consistent with the pharmacokinetic characteristics observed in healthy subjects, as indicated in Figure 13.

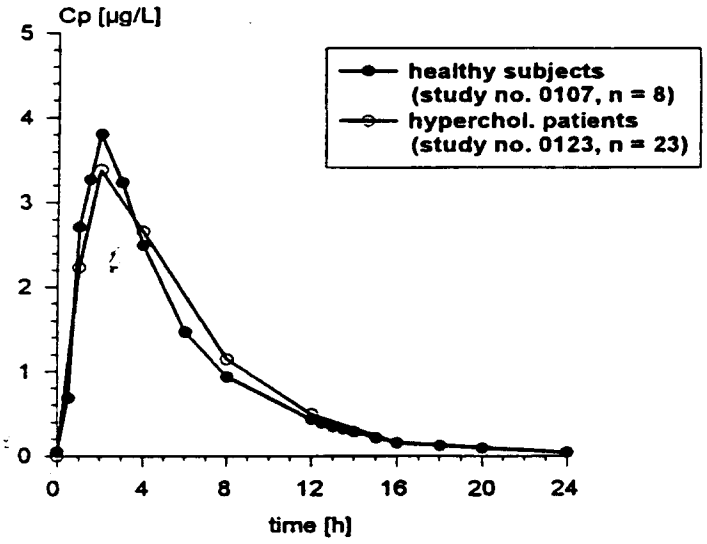


FIGURE 13. Cerivastatin plasma concentrations (g. Means) assayed [redacted] on day 7 (healthy subjects) or on day 5 (hypercholesterolemic patients) of a 300 µg q.d. dose regimen

There was no correlation between the pharmacokinetic parameters and pharmacodynamic measurements. Pharmacokinetic measurements were taken after the 5th daily dose. The lipid measurements that most closely corresponded to that time was Day 7. This was used by the reviewer because of the assumption of steady-state for cerivastatin.

APPEARS THIS WAY
ON ORIGINAL

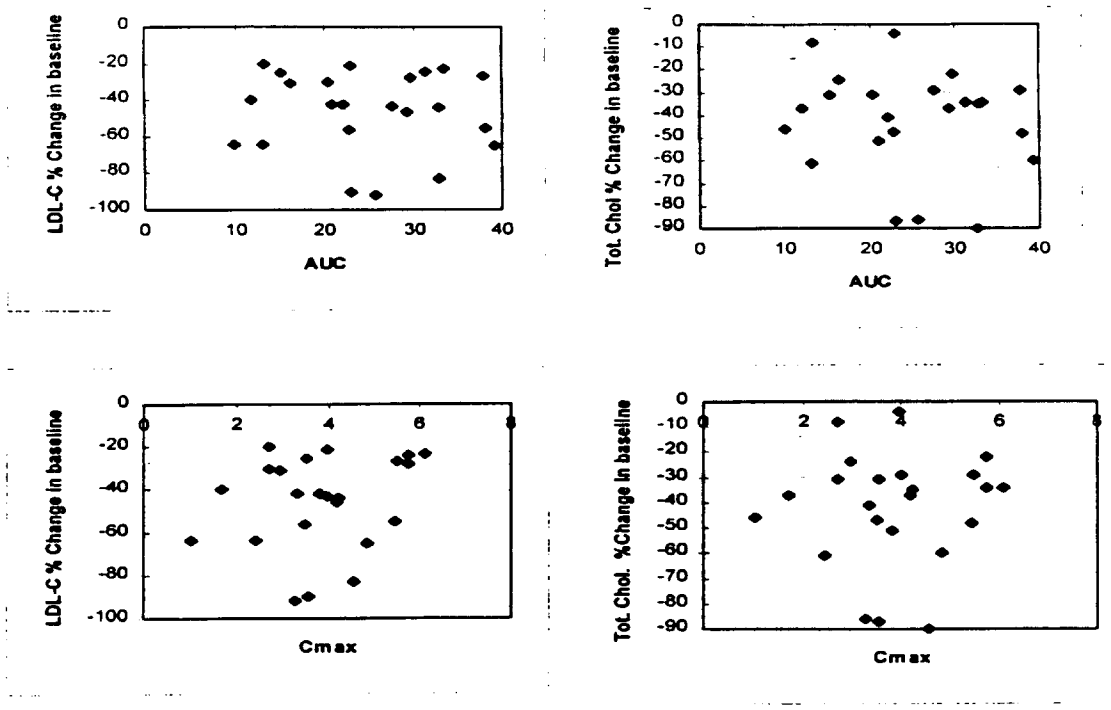


FIGURE 14. Relationships between percent change of LDL-C (Friedewald) from baseline and AUC and Cmax values for cerivastatin at 300 µg.

In the double-blind dose ranging study no. 0124 (pivotal efficacy trial) where doses of 50 μg, 100 μg, 200 μg and 300 μg cerivastatin once daily were given to patients with hypercholesterolemia, cerivastatin plasma concentrations at 12 hours post dose were drawn from 116 patients at several visits. Analysis was done on the 86 patients valid for efficacy who received active drug. The number of patients in each treatment group and the mean plasma concentrations are presented in Table 45.

Table 45

Mean cerivastatin plasma concentrations [μg/L] and correlation with %-change in LDL-cholesterol

Cerivastatin dose [μg]	N	Visit 5	Visit 6	Visit 7	Visit 8	Visit 10	Visit 16
50	20	0	0.15	0.15	0.16	0.14	0.13
100	22	0	0.21	0.21	0.24	0.22	0.26
200	24	0	0.40	0.34	0.33	0.39	0.48
300	20	0	0.55	0.92	0.80	0.76	0.61
Correlation		- 0.32	- 0.23	- 0.31	- 0.35	- 0.40	
R-Square		0.11	0.06	0.10	0.13	0.16	

The plasma concentrations were in the same range as those determined for volunteers. There was no apparent accumulation of cerivastatin beyond Visit 6, as expected from its relatively short half-life (2-5 hours). Also, the mean plasma concentrations of cerivastatin at 12 hours post dose increased with increasing dose.

Correlations between percent change from baseline in LDL-cholesterol and trough plasma concentrations of cerivastatin were calculated at each visit. Although the correlations were low, the linear fit of plasma concentration to percent change in LDL-cholesterol was significant at each visit: LDL-cholesterol was inversely related to cerivastatin plasma concentration.

The decrease in pharmacodynamic values were dose-dependent with greater reduction occurring at higher dosages of cerivastatin (Table 46).

Table 46. Cerivastatin Least Squares Means % Change in Lipids at Endpoint for Efficacy Population

Parameters	50 µg N=145	100 µg N=136	200 µg N=138	300 µg N=137
HDL-C	5.7%	6.8%	9.8%	9.0%
Total -C	-9.6%	-12.9%	-17.8%	-19.9%
LDL-C	-13.5%	-18.9%	-25.6%	-28.6%

No differences in the overall occurrence of adverse events with increasing dosage were observed. However, the more serious adverse events occurred at the 300 µg dose. The most common adverse events were pharyngitis, rhinitis and headache. A slight increase in rhinitis was observed with increasing dosage.

Subgroup analyses indicated that females had larger observed decreases in LDL-C than males, as did non- or moderate drinkers. As mentioned previously, this gender difference is the opposite of what was observed in the healthy volunteers. The older groups had larger decreases in LDL-C. The age and gender differences were probably due to higher exposure to the drug because the mean body weights were less compared to males and a younger population (see Figure 15).

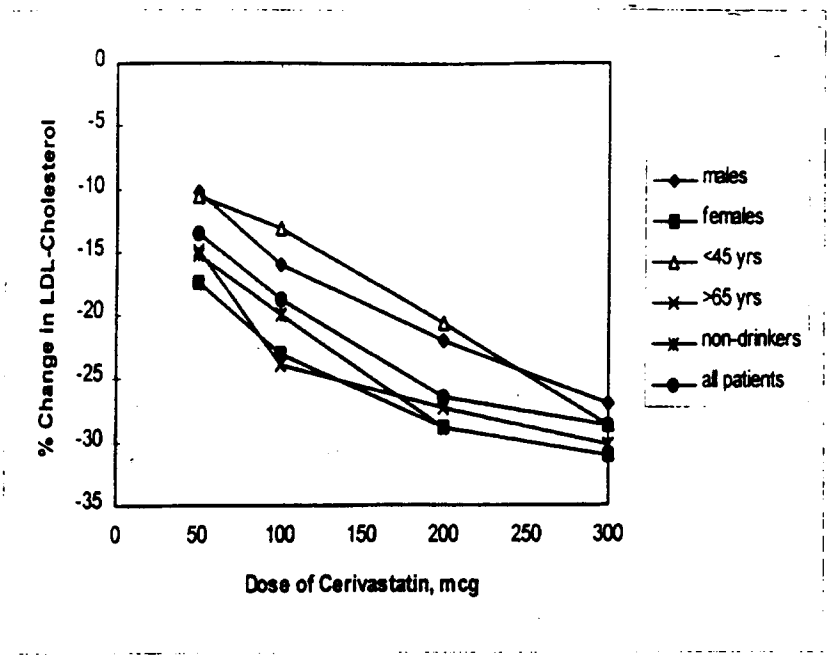


FIGURE 15. Comparison of sub-group analyses.

Similarly, in study no. 0110 individual trough plasma concentrations at steady-state, evaluated for 89 patients valid for efficacy, did not show any time-dependent changes over the four-week treatment. In addition, dose proportionality could be shown with a mean trough plasma concentration of 0.21 μg/L during 100 μg cerivastatin treatment and 0.4 μg/L during 200 μg cerivastatin treatment.

APPEARS THIS WAY
ON ORIGINAL

LABELING COMMENTS:

1. The sponsor makes a statement regarding the concomitant administration of certain classes of medications during the clinical trials. If a sub-group analysis has not been conducted and if sufficient number of subjects have not been exposed to these drugs, the section on OTHER CONCOMITANT THERAPY should not be allowed in the package insert.

2. See attached revised package insert.

4/21/97
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 4/25/97
FT initialed by Hae-Young Ahn, Ph.D., Team Leade 5/12/97

cc: NDA 20-740 (1 copy), HFD-510(Orloff, Simoneau, Barbehenn), HFD-340 (Vishwanathan), HFD-870(Ahn, Jones, M. Chen), CDR(Murphy).

Appendix

Proposed Package Insert

Summary Tables

Study Summaries

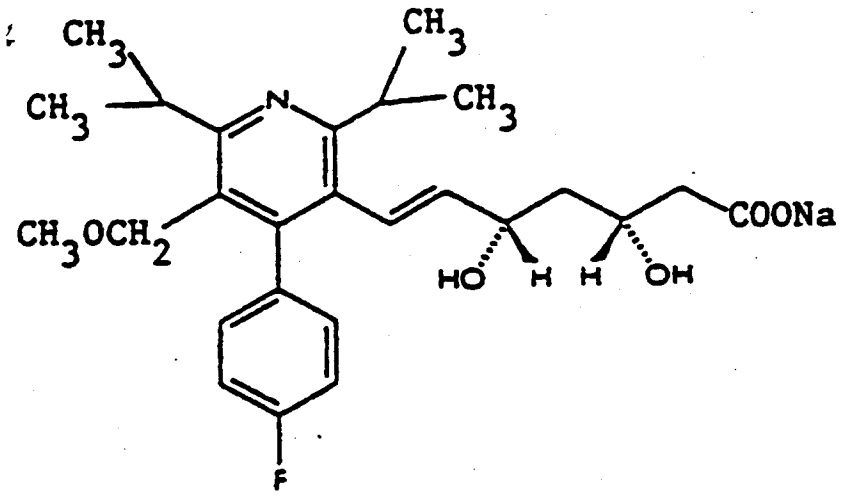
APPEARS THIS WAY
ON ORIGINAL

BAYCOL®

CAUTION: Federal law prohibits dispensing without prescription.

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, 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, and is in part structurally distinct from the fungal derivatives of this therapeutic class. 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 0.05, 0.1, 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, methylhyroxypropylcellulose, polyethylene glycol, and titanium dioxide.

CLINICAL PHARMACOLOGY

Multiple epidemiologic studies have established that elevated serum cholesterol, specifically elevated low density lipoprotein cholesterol (LDL-C), and decreased high density lipoprotein cholesterol (HDL-C) are risk factors for the development of cardiovascular disease. The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) was a multi-center, randomized, double-blind study involving 3,806 asymptomatic middle-aged men in the United States with Type II hyperlipoproteinemia treated with diet and cholestyramine. Results of this trial demonstrated that a statistically significant reduction of 19% in the incidence of definite myocardial infarction and/or coronary heart disease death was associated with an 8% decrease in blood cholesterol and an 11% decrease in LDL-C levels.[1,2] Recent studies have shown that HMG-CoA reductase inhibitors significantly reduce the incidence of myocardial infarction and death from cardiovascular causes in men with moderate hypercholesterolemia and no history of myocardial infarction and have shown significant reduction in all-cause mortality, especially that from coronary disease, in men and women with hypercholesterolemia and angina pectoris or previous myocardial infarction.[3,4]

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 cerivastatin-induced changes in plasma lipoprotein levels on the evolution of atherosclerosis in humans has not been established.[5]

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.[6]

Pharmacokinetics

Absorption

BAYCOL™ (cerivastatin sodium tablets) is administered orally in the active form. The absolute bioavailability of cerivastatin following a 0.2 mg tablet oral dose is 60% (range 39 - 101%).[7] 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.[8,9,10,11,12] The bioavailability of cerivastatin sodium tablets is equivalent to that of a solution of cerivastatin sodium.[7] No unchanged cerivastatin is excreted in feces[13].

Cerivastatin exhibits linear kinetics over the dose range of 0.05 to 0. 3 mg daily.[8,14] 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.[14,15] AUC values are also dose–proportional over this dose range and the mean time to maximum concentration (t_{max}) is approximately 2.5 hours for all dose strengths.[14,15] Following oral administration, the terminal elimination half-life ($t_{½}$) for cerivastatin is 2 to 3 hours.[14,15] Steady-state plasma concentrations show no evidence of cerivastatin accumulation following administration of up to 0. 40 mg daily for 7 days.[3]

Results from an overnight pharmacokinetic evaluation following single-dose administration of cerivastatin with the evening meal or 4 hours after the evening meal showed[10] 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,[20] either at mealtime or at bedtime, there were no differences in the lipid-lowering effects of cerivastatin . Both regimens of 0.2 mg qd were slightly more efficacious than 0.1 mg bid.

Distribution

The volume of distribution (VD_{ss}) is calculated to be 0.3 L/kg.[7] 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.[16]

Metabolism

Biotransformation pathways for cerivastatin in humans include the following : demethylation of the benzylic 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

of renal impairment was not evident since the mean cerivastatin levels in the mildly and moderately impaired groups were at least as high as in the severely impaired group. The elimination half-life was only slightly increased in the patients with renal impairment.

Hepatic Insufficiency: Cerivastatin pharmacokinetics have not been studied in patients with hepatic insufficiency. 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).

Race: Based on the pooled analysis of data from studies performed in Caucasian, Japanese and Black subjects, no differences in AUC, C_{max}, t_{max} and ($t_{½}$) were observed.

Drug Interactions

ANTACID (Magnesium-Aluminum Hydroxide): The influence of antacid on the pharmacokinetics of cerivastatin sodium was evaluated in 8 healthy males in a randomized 2-way crossover study.[34] Concurrent dosing of 0.2 mg cerivastatin sodium and 10 ml of antacid suspension resulted in an approximate 10% decrease in the cerivastatin AUC and C_{max} when compared to dosing cerivastatin sodium alone. This small decrease in cerivastatin plasma concentrations is not expected to be clinically significant.

CIMETIDINE: Cimetidine is a potent inhibitor of the hepatic P-450 enzyme system; it is known to significantly increase the plasma levels of many drugs, including some members of the 'statin' class of cholesterol-lowering drugs. The influence of cimetidine on the pharmacokinetics of cerivastatin sodium was evaluated in 8 healthy males in a randomized 2-way crossover study.[35] Concomitant administration of 0.2 mg cerivastatin sodium with 400 mg cimetidine resulted in a small decrease in the cerivastatin AUC (11%) and C_{max} (7%) when compared to cerivastatin sodium dosing alone, an effect not expected to be clinically significant.

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[36], 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,[37] 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 19% and 8%, respectively; and a decrease in C_{max} of about 30% when compared to dosing cerivastatin sodium alone. Therefore, it would be expected that a dosing

and M23 metabolites.[17] The relative potencies of metabolites M1 and M23 are approximately 50% and 80% of the parent compound, respectively.[18] 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.[19] 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 cerivastatin to healthy volunteers,[13] 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 i.v. dosing is 12 to 13 liters per hour.[7]

Special Populations

Gender and Geriatric: The effects of gender and age on the pharmacokinetics of cerivastatin were evaluated in a 3-arm study in which young and elderly males and elderly females were enrolled. All subjects were administered 0.2 mg cerivastatin sodium daily, immediately after the evening meal for 7 days. Results from an overnight pharmacokinetic evaluation in this study showed that concentrations of cerivastatin do not vary significantly as a function of either age or gender.[12]

Pediatric: Cerivastatin pharmacokinetics have not been studied in patients < 18 years of age.

Renal Insufficiency: In a clinical pharmacology study,[19], a single 0.3 mg dose of cerivastatin sodium was given to 6 healthy young males, and to 18 patients with renal insufficiency ranging from mild to severe. Plasma levels of cerivastatin were consistently higher in the patients with renal impairment, with mean cerivastatin levels approximately 50% higher in the severely impaired group compared to healthy controls. A clear relationship of plasma drug level to degree

schedule of cerivastatin sodium given qhs and cholestyramine given before the evening meal would not result in a significant decrease in the clinical effect of cerivastatin sodium.

DIGOXIN: The effect of cerivastatin sodium on the steady-state levels of digoxin was evaluated in a multiple dose study in 13 young healthy males.[38] After 14 days of concurrent dosing of 0.2 mg cerivastatin sodium and 0.25 mg digoxin, there was less than a 10% increase in plasma digoxin levels and a 6% decrease in digoxin clearance when compared to corresponding steady-state values following digoxin alone. Patients taking digoxin should be monitored appropriately when cerivastatin sodium therapy is initiated, especially at higher doses which have not been evaluated. This study also showed that digoxin did not alter the AUC of cerivastatin but increased C_{max} 20%.

WARFARIN: The influence of cerivastatin sodium on the pharmacokinetics of warfarin was evaluated in 24 healthy males in a randomized, double-blind 2-way crossover study.[39] A single 25 mg dose of sodium warfarin was given after a 4-day treatment period of either 0.3 mg cerivastatin sodium or placebo. The AUC and the C_{max} of both the (R) and (S) isomers of warfarin were unaffected by concurrent dosing of cerivastatin sodium. Additionally, the mean prothrombin time and the mean clotting factor VII activity were unchanged when comparing concurrent warfarin-cerivastatin sodium dosing against concurrent warfarin-placebo dosing. This study also showed that warfarin did not alter the pharmacokinetics of cerivastatin sodium.

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.[5] A response in Total- C and LDL-C was evident by one week and the maximum therapeutic response occurred within four weeks.[21,22] The response was maintained with chronic therapy.[23] Over 2,800 patients with Type IIa and IIb hypercholesterolemia were treated in trials of 4 to 104 weeks duration.[24] In a large 24 week, randomized, double-blind, placebo-controlled trial done in 695 patients in the US, BAYCOL™ (cerivastatin sodium tablets) produced dose-related reductions in plasma LDL-C and Total-C. Clinically significant reductions in plasma triglycerides (TG) and increases in HDL-C were also observed in this study as shown in Table 1.[25]

Table 1

Dose Response in Patients With Primary Hypercholesterolemia[26]

(Mean Percent Change from Baseline to Endpoint)

Dosage	n	Total-C	LDL-C	HDL-C	TG
Placebo	139	+1.7	+1.9	+2.5	+1.5
BAYCOL™					
0.05 mg qd	145	-9.6	-13.5	+5.7	-5.6
0.1 mg qd	136	-12.9	-18.9	+6.8	-5.0
0.2 mg qd	138	-17.8	-25.6	+9.8	-10.1
0.3 mg qd	137	-19.9	-28.5	+9.0	-14.0

In a dose-scheduling study, BAYCOL™ (cerivastatin sodium tablets) given as a 0.2 mg dose once daily with dinner or at bedtime was shown to be equally efficacious, and superior to a regimen of 0.1 mg given twice daily (Table 2).[27]

Table 2

Effects of **BAYCOL™** Dose-Scheduling on Plasma LDL-C Response

(Mean Percent Change from Baseline After 28 Days)

Dosage	n	LDL-C
Placebo	45	+1.4
BAYCOL™		
0.1 mg bid	89	-25.7
0.2 mg qpm	88	-29.4
0.2 mg qhs	86	-30.4

bid = twice daily

qpm = with dinner

qhs = at bedtime

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 (Types IIa and IIb), when the response to dietary restriction of saturated fat and cholesterol and other nonpharmacological measures alone has been inadequate.[28,29]

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:

$$\text{LDL-C} = [\text{Total-C}] \text{ minus } [\text{HDL-C} + \text{TG}/5]$$

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 and dosage adjusted according to the patient's response to therapy.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:[28,29]

	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 (< 0.91mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).

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.

Cerivastatin has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL, i.e., hyperlipoproteinemia types I, III, IV, or V.***

*** Classification of Hyperlipoproteinemias

		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.

The effect of cerivastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality has not been established.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

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

Pregnancy and lactation. Atherosclerosis is a chronic process, and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. 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.

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.[30]

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 with acute renal failure secondary to myoglobinuria have been reported with other HMG-CoA reductase inhibitors. This has not been reported with cerivastatin sodium to date. 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.[31] 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 another HMG-CoA reductase inhibitor was found to be increased if therapy with cyclosporine, gemfibrozil, erythromycin. or niacin was administered concurrently.

Uncomplicated myalgia has been observed infrequently in patients treated with cerivastatin sodium at rates that could not be distinguished from placebo.[32]

The use of fibrates alone may occasionally be associated with myopathy. The combined use of HMG-CoA inhibitors and fibrates should generally 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.[33]

Homozygous Familial Hypercholesterolemia

Cerivastatin sodium has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this patient group, it has been reported that HMG-CoA reductase

inhibitors are less effective because these patients 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, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin: See 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.

Cerivastatin sodium demonstrated no effect upon non-stimulated cortisol levels and no effect on thyroid metabolism as assessed by TSH.[41] 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, e.g., ketoconazole, spironolactone, or cimetidine, that may decrease the

levels of endogenous steroid hormones.

CNS and other Toxicities

Chronic administration of cerivastatin to rodent and non-rodent species demonstrated the principal toxicological targets and effects observed with other HMG-CoA reductase inhibitors[41]: Hemorrhage and edema in multiple organs and tissues including CNS (dogs); cataracts (dogs); degeneration of muscle fibers (dogs, rats and mice); hyperkeratosis in the nonglandular stomach (rats and mice, this organ has no human equivalent); liver lesions (dogs, rats and mice). The effects are considered secondary to an exaggerated pharmacological activity of cerivastatin at high doses.

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}), which were about 23 times higher than the mean values in humans taking 0.3 mg/ day.[42,43] No CNS lesions were observed after chronic treatment with cerivastatin for up to two years in the mouse (at doses up to 55 mg/kg/day) and rat (at doses up to 0.158 mg/kg/day) and for one year in the monkey (at doses up to 0.1 mg/kg/day).[42]

Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year study was conducted in rats at average daily doses of cervastatin 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.[42,43] Tumor incidences of treated rats were comparable to controls in all treatment groups.[44,45] A carcinogenicity study conducted in mice with average daily doses of cervastatin of 0.4, 1.8, 9.1, or 55 mg/kg for 24 months revealed an increased incidence of hepatocellular adenomas in males and females, and of hepatocellular carcinomas in males from the 9.1 and 55 mg/kg dose groups.[42,46] Analytical results of plasma samples from cerivastatin treated mice in this bioassay were highly variable compared to other species. Therefore, interspecies extrapolation based on multiples of exposure is not meaningful.[42,43]

No evidence of mutagenicity was observed *in vitro* with or without metabolic activation in the following assays:[42,47] 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 mutagenicity *in vivo* in either a mouse Micronucleus Test or 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.[42,48] At a dose of 0.3 mg/kg/day (plasma C_{max} 4 - 5 times the human level), a marginal reduction in fetal weight and delay in bone development was observed; the length of gestation was marginally prolonged, stillbirths were increased, and the survival rate up to day 4 postpartum was decreased. In the testicles of dogs treated chronically with cerivastatin, atrophy, vacuolization of the germinal epithelium, and spermatidic giant cells were observed. Semen analysis in dogs revealed an increased number of morphologically altered spermatozoa, but this was reversible when drug administration was discontinued.[42,49]

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS

Safety in pregnant women has not been established. Cerivastatin was not teratogenic and did not promote developmental toxicity in rats at oral doses up to 0.72 mg/kg, and in rabbits at oral doses of up to 0.750 mg/kg.[42,50] These doses resulted in plama levels (C_{max}) 6- 7 times the human exposure (human dose 0.3 mg) for rats and 3 - 4 times the human exposure for rabbits.[43] 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 cogenital anomalies have been received following intrauterine exposure to other HMG-CoA reductase inhibitors.[51] If a woman becomes pregnant while taking cerivastatin, it should be discussed and the patient advised again as to potenial hazards to the fetus.

Nursing Mothers

Based on preclinical data, cerivastatin is present in breast milk in a 1.3:1 ratio (milk:plasma).[52] 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 individuals less than 18 years old have not been established. Treatment in patients less than 18 years of age is not recommended.

Geriatric Use

There were no clinically relevant effects of age on the pharmacokinetics of cerivastatin sodium.[11,12]

Renal Insufficiency

Patients with renal impairment should be administered BAYCOL with caution and clinically monitored with appropriate dosage adjustment, if necessary.

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.

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.[53] Adverse reactions have usually been mild and transient.[54] Cerivastatin sodium has been evaluated for serious adverse events in more than 3,000 patients and is generally well-tolerated.[55]

Clinical Adverse Experiences

Adverse experiences occurring with a frequency >2%, regardless of causality, in U.S. placebo-controlled clinical studies, are shown in the table below:[56]

Adverse Event	BAYCOL™ (cerivastatin sodium tablets) (n=1,063)	PLACEBO (n=247)
Body as a Whole		
Headache	10.9%	12.6%
Flu Syndrome	7.2%	8.1%
Accidental Injury	6.5%	6.9%
Back Pain	4.6%	6.1%
Abdominal Pain	3.9%	3.6%
Asthenia	3.2%	2.8%

Chest Pain	2.7%	2.8%
Leg Pain	2.4%	1.2%
Digestive		
Dyspepsia	4.9%	4.9%
Diarrhea	4.5%	3.6%
Flatulence	3.3%	3.6%
Nausea	2.5%	3.2%
Musculoskeletal		
Arthralgia	7.3%	4.5%
Myalgia	2.2%	1.2%
Nervous		
Dizziness	2.6%	3.6%
Insomnia	2.1%	1.2%
Respiratory		
Pharyngitis	13.2%	17.0%
Rhinitis	11.5%	12.1%
Sinusitis	7.3%	5.7%
Cough Increased	2.5%	2.0%
Bronchitis	2.4%	1.6%
Skin and Appendages		
Rash	4.0%	5.7%

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

Skeletal: myopathy, muscle cramps, rhabdomyolysis, arthralgias.

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.

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, 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.

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.[57] Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, 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.[5,9]

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.)[28,29]

The recommended starting dose is 0.05 mg or 0.1 mg once daily in the evening. The recommended dosing range is 0.05 - 0.3 mg as a single dose in the evening.[58] Cerivastatin sodium may be taken with or without food since there are no apparent differences in the lipid lowering effects of cerivastatin sodium administered with the evening meal or at bedtime[59] Dosages should be individualized according to the recommended goal of therapy (see NCEP Guidelines) and the patient's response.

Since the maximal effect of a given dose of cerivastatin sodium is seen within 4 weeks,[60] periodic lipid determinations should be performed at this time and the dosage adjusted to the patient's response to therapy and established treatment guidelines.

Concomitant Therapy

The lipid-lowering effects on LDL-C and Total-C are additive when cerivastatin sodium is combined with a bile acid exchange resin.[61] When co-administering cerivastatin sodium and a bile acid exchange resin, e.g., cholestyramine, cerivastatin sodium should be given at least $\geq$ 4 hours after following the resin to avoid an interaction due to drug binding to the resin. (*See also* ADVERSE REACTIONS: *Concomitant Therapy.*)

Dosage in Patients with Renal Insufficiency

Patients with a clinical diagnosis of renal disease should follow the standard dosing recomendation and begin BAYCOL™ (cerivastatin sodium tablets) treatment at 0.05 or 0.1 mg daily. Patients with advanced renal disease should be started at the low end of the recommended dosing range and closely monitored.[19]

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

HOW SUPPLIED

BAYCOL™ (cerivastatin sodium tablets) is supplied as 0.05 mg, 0.1 mg, 0.2 mg, and 0.3 mg tablets. The different tablet strengths can be identified as follows:

Strength	Color	Markings
0.05 mg	white	BAY 281
0.1 mg	pale yellow	BAY 282
0.2 mg	light yellow	BAY 283
0.3 mg	yellow brown	BAY 284

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

Bottles of 100: 0.05 mg (NDC 0026-2881-51)
0.1 mg (NDC 0026-2882-51)
0.2 mg (NDC 0026-2883-51)
0.3 mg (NDC 0026-2884-51)

Bottles of 2000: 0.05 mg (NDC 0026-2881-74)
0.1 mg (NDC 0026-2882-74)
0.2 mg (NDC 0026-2883-74)
0.3 mg (NDC 0026-2884-74)

Unit Dose

Packages of 100: 0.05 mg (NDC 0026-2881-48)
0.1 mg(NDC 0026-2882-48)
0.2 mg (NDC 0026-2883-48)
0.3 mg (NDC 0026-2884-48)

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

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

	REFERENCES	NDA LOCATION	
		Volume	Page(s)
1	Lipid Research Clincs Program: The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence in coronary heart disease. *J Am Med Assoc* 251, 351-364 (1984).		
2	Lipid Research Clincs Program: The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *J Am Med Assoc* 251, 365-374 (1984).		
3	The West of Scotland Coronary Prevention Group. Prevention of coronary heart disease in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.		
4	The Scandanavian Simivastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandanavian Simvastatin Survival Study (4S)..*Lancet* 1994;344:1383-9.		
5	Section 8.7 Integrated Summary of Efficacy	675	1-205
6	Schmidt, D. Inhibition of HMG-CoA reductase by BAY w 6228. BAYER AG Report No. 19,618 October 12, 1990.		
7	Ochmann,K., Ritter,W., Unger,S. Investigation of the absolute bioavailability of BAY w 6228 after single administration of 100 µg iv as a bolus in comparison to 200 µg p.o.	165 166	1 - 259 1 - 187
8	Mazzu,A., Lettieri,J., Heller,A., Collins,S., Kaiser,L., Birkett,P. A controlled double-blind, parallel group ascending, single dose study of the safety and tolerability of the HMG-CoA reductase inhibitor BAY w 6228. Study No. 0106 (US	171 172	1 - 374 1 - 366
9	Mazzu,A., Lettieri,J., Heller,A., Collins,A., Kaiser,L., Birkett,A. A controlled double-blind, parallel group ascending, single dose study of the safety and tolerability of the HMG-CoA reductase inhibitor BAY w 6228. Study No. 0107 (US	177 178 179 180	1 - 326 1 - 404 1 - 333 1 - 219
10	Kumor,K. An open randomized 4-way crossover study of the safety, tolerability and pharmacokinetics of 200 µg BAY w 6228 given as morning or evening doses under fasted or fed conditions.	190 191 192	1 - 227 1 - 325 1 - 150
11	Mazzu,A., Lettieri,J., Collins,S., Kaiser,L., Birkett,P., Hogan,C. A controlled double-blind parallel group, multiple-dose study of the safety, tolerability and pharmacokinetics of the HMG-CoA reductase inhibitor BAY w 6228 in young vs elderly volunteers.	193 194 195 196	1-397 1-159 1-280 1-221

	REFERENCES	NDA LOCATION	
		Volume	Page(s)
12	Mazzu,A., Amand,R., Lettieri,J., Kaiser,L., Birkett,J.P., Collins,S., Heller,A. A controlled double-blind parallel group multiple-dose study of the safety, tolerability and pharmacokinetics of the HMG-CoA reductase inhibitor BAY w 6228 in male vs female volunteers.	197 198 199 200 201	1-197 1-223 1-328 1-202 1-265
13	Wingender,W., Mück,W., Unger,S., Göller,G., Radtke,M., Rohde,E., Kuhlmann,J. Elucidation of the metabolism, determination of the excretion pattern and the excretion balance after a single oral administration of [^{14}C]BAY w 6228. Non-blinded, non-controlled study.	169 170	1-304 1-116
14	Mazzu,A., Lettieri,J.T., Fiebach,M.Z. A study to evaluate the dose proportionality of 100 µg, 200µg, and 300 µg BAY w 6228 tablets.	185 186	1-375 1-350
15	Mazzu,A.L., Lettieri,J.T., Cole,S. A study to evaluate the dose proportionality of 50 µg and 100 µg BAY w 6228 tablets and the dose strength equivalence of one 100 µg versus two 50 µg BAY w 6228 tablets.	225 226	1-348 1-234
16	Ahr,H.J. [^{14}C]BAY w 6228: Investigation of the binding to plasma proteins: characteristics of the binding and interaction studies in vitro.	181	18-43
17	Section 5.3 Nonclinical Absorption, Distribution, Metabolism and Excretion (p. 42-43)	15	203,204
18	Data of File		
19	Schmage,N., Mück,W., Heyen,P. A non-blinded study with different degrees of renal impairment compared to healthy volunteers to assess potential differences of pharmacokinetic parameters after single-dose administration of BAY w 6228 300 µg. APPEARS THIS WAY ON ORIGINAL	202 203 204 205	1-265 1-188 1-160 1-304
20	Jungerwirth,S., Whalen,A., Allenby,K., Perelli,V.S. A double-blind placebo-controlled dose scheduling study of BAY w 6228 in doses of 100 µg twice daily with breakfast and dinner compared to 200 µg once daily with dinner or at bedtime in patients with hypercholesterolemia.	192	151
21	Section 8.7 Integrated Summary of Efficacy (p84).	675	93

REFERENCES		NDA LOCATION	
		Volume	Page(s)
22	A double-blind, dose-ranging study of BAY w 6228 in doses of 50 µg, 100 µg 200µg, and 300 µg once daily compared to placebo and to Lovastatin 40 mg once daily in patients with hypercholesterolemia.	230-320	---
23	Section 8.7 Integrated Summary of Efficacy (p 54,84).	675	62, 93
24	Section 8.7 Integrated Summary of Efficacy (p.3; 6B-6E).	675	4, 9-12
25	Section 8.7 Integrated Summary of Efficacy (p 11-15).	675	19-23
26	Section 8.7 Integrated Summary of Efficacy (p 12-13)	675	20-21
27	Section 8.7 Integrated Summary of Efficacy (p30-32).	675	38-40
28	The expert Panel: Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Acults. *Arch Intern Med* 148,36-69 (1988).		
29	Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *J Am Med Assoc* 269,3015-3023 (1993).		
30	Section 8.8.2 Integrated Summary of Safety (p84,85).	676	103, 104
31	Section 8.8.2 Integrated Summary of Safety (p69).	676	88
32	Section 8.8.2 Integrated Summary of Safety (p10,13).	676	29, 32
33	Section 8.8.2 Integrated Summary of Safety (p 65,72,79).	676	84, 91, 98
34	Dietrich,H., Ritter,W., Wingender,W., Unger,S., Ochmann,K. Influence of Maalox® 70 on the pharmacokinetics of BAY w 6228.	206	29-393
35	Frey,R., Ritter,W., Unger,S., Ochmann,K., Wingender,W. Investigation on the influence of cimetidine on the pharmacokinetics of BAY w 6228.	207	1-336
36	Frey,R., Ritter,W., Unger,W., Lemm,G., Ochmann,K. Influence of cholestyramine on the pharmacokinetics of BAY w 6228.	209 210	1-298 1-111
37	Wetzelsberger,N., Fuder,H., Stiegler,S. Study on the influence of a pretreatment with cholestyramine in the pharmacokinetics of BAY w 6228 after oral administration of both drugs at different time points in healthy male volunteers.	211	1-340
38	Mazzu,A., Lettieri,J., Heller,A., Collins,S., Kaiser,L., Birkett,J. A study to evaluate the potential reciprocal interaction between BAY w 6228 and Digoxin.	212 213 214	1-208 1-335 1-244

REFERENCES		NDA LOCATION	
		Volume	Page(s)
39	Müller,F.O., Duursema,L., Middle,M.V., Schall,R., Hundt,H.K.L. A randomized, double-blind cross-over trial to determine the effects of BAY w 6228 on the pharmacokinetics of a single-dose on concomitantly administered warfarin on the steady-state pharmacokinetics of BAY w 6228, in healthy male volunteers.	215 216 217	1-205 1-361 1-310
40	Section 8.8.2 Integrated Summary of Safety (p100-105).	676	119-124
41	Section 8.8.2 Integrated Summary of Safety (p88-90).	676	107-109
42	Section 2.5 Non-clinical Pharmacology and Toxicology Summary (p37)	2	39
43	Section 2.5 Non-clinical Pharmacology and Toxicology Summary (p52)	2	54
44	Section 2.5 Non-clinical Pharmacology and Toxicology Summary (p16)	2	18
45	Section 5.2 Non-clinical Pharmacology and Toxicology Summary (p29)	15	80
46	Section 5.2 Non-clinical Pharmacology and Toxicology Summary (p10)	15	61
47	Section 5.2 Non-clinical Pharmacology and Toxicology Summary (p70)	15	121
48	Section 5.2 Non-clinical Pharmacology and Toxicology Summary (p64)	15	115
49	Section 5.2 Non-clinical Pharmacology and Toxicology Summary (p39)	15	90
50	Section 5.2 Non-clinical Pharmacology and Toxicology Summary (p63)	15	114
51	Physicians Desk Reference - Package Inserts for LESCOL®(fluvastatin sodium), MEVACOR®(lovastatin), PRAVACHOL®(pravastatin sodium), ZOCOR®(simvastatin)		
52	Section 2.5 Non-clinical Pharmacology and Toxicology Summary (p48)	2	50
53	Section 8.8.2 Integrated Summary of Safety (p34,38).	676	53, 57
54	Section 8.8.2 Integrated Summary of Safety (p10,11).	676	29, 30
55	Section 8.8.2 Integrated Summary of Safety (p45-51).	676	64-70
56	Section 2.10 Risk Benefit (p8).	2	8
57	Section 8.8.2 Integrated Summary of Safety (p105-107).	676	124-126
58	Section 8.7 Integrated Summary of Efficacy (p30-32,92,107-108).	675	101-116, 117
59	Section 8.7 Integrated Summary of Efficacy (p30-32, 80-82).	675	38-40, 89-91
60	Section 8.7 Integrated Summary of Efficacy (p84).	675	93
61	Section 8.7 Integrated Summary of Efficacy (p55-57).	675	63-65