Section 8
Safety review: Cerivastatin
Introduction

The overall approach to the assessment of the safety of cerivastatin recognizes that this drug is a member of the well-characterized class of HMGRIs. While it differs markedly in structure from the fungal-derived HMGRIs, it shares the same mechanism of action through inhibition of the rate-limiting enzyme in cholesterol biosynthesis. To the extent that any toxicities of the class are related to this mechanism of therapeutic action, some or all of the safety concerns attributed to other agents obviously pertain. The principal, potentially serious adverse effects associated with other statins are in the liver with elevations in transaminases, and in the muscle with myalgia, CK elevations, and, rarely, frank rhabdomyolysis.

As a rule, with other drugs in this class, the hepatic effects are seen relatively early in the course of treatment (i.e., in the first 6 months) denoting perhaps an individual susceptibility phenomenon that if present, declares itself after relatively short exposures. For certain of the statins, the incidence of transaminase elevations has been dose-related and thus correlated with the degree of cholesterol lowering. As such, like cholesterol lowering, leakage of transaminases may be a marker of the extent of the drug's pharmacologic effect in the liver. By example, to date, the drug for which the dose-related hepatic effects have been most marked is atorvastatin, currently the statin approved for marketing at doses that effect the greatest reductions in TC, LDL-C, and TG. On the other hand, in recent large-scale long-term placebo-controlled trials of two other statins (pravastatin and simvastatin) at approved doses less potent than the higher doses of atorvastatin, the best predictor of significant LFT elevations was not, as might have been expected, treatment group, but rather baseline or early treatment LFTs (normal versus abnormal). Based on the relatively low lipid altering potency of cerivastatin at the doses proposed for marketing, marked hepatic adverse effects would not be anticipated.

With regard to muscle effects, within this class of drugs, in susceptible individuals, these appear to be associated with increases in circulating levels of HMGRIs and may be due to depletion of muscle cell coenzyme Q in the face of above-threshhold systemic exposure. In theory, the resultant disruption of cellular energy metabolism can result in cell dysfunction or frank cell death. Under normal circumstances, there is extensive first-pass hepatic metabolism of the statins, with the pharmacodynamic effect as well being mediated via a hepatic site of action. Most cases of rhabdomyolysis have occurred in patients taking a statin in conjunction with another agent that tends to impair hepatic clearance and augment the systemic exposure. Typically, these are agents that inhibit the cytochrome P450 isozyme, 3A4, responsible for metabolism of most members of the statin class. Thus, cyclosporine, fibric acid derivatives, erythromycin, and intraconazole have all been implicated in HMGRI-induced rhabdomyolysis and are relatively contraindicated in patients taking HMGRIs. The incidence of rhabdomyolysis is thought also to be increased with concomitant use of niacin, though this interaction and its mechanism are less well characterized.

In addition, though it has not proved to be a problem in humans, because of an observed induction of lenticular opacities in dogs treated with lovastatin, the first approved HMGRI, the

ophthalmologic effects of cerivastatin were investigated by the sponsor and will be addressed briefly in this review. Furthemore, because statins do inhibit cholesterol synthesis, the effects of cerivastatin on testicular and adrenal function were also investigated and will likewise be reviewed. This has not been a problem with other statins, thought to be because of the fact that adrenal and gonadal tissue utilize as steroid precursor cholesterol that is not endogenously sythesized, but derive it from LDL particles via LDL-receptors or from HDL via a specific HDL docking receptor.

Finally, while the pharmacokinetics of cerivastatin at the doses proposed for marketing raise no hypothetical safety concerns that would distinguish this drug from the other members of the class, whether the unique potency (per weight of drug) of cerivastatin in inhibiting HMG-CoA reductase (coupled with as yet unknown quirks of clearance at higher doses) will lead to increased systemic effects as the dose is further extended remains to be seen.

Structure of the sponsor's safety summary

This NDA contains data from clinical trials of short (up to 32 weeks) and long (extensions of up to two years) duration. In addition, studies were conducted in the U.S. and outside the U.S. The sponsor has chosen to pool and analyze the safety data in this NDA according to duration of exposure and has presented separately the safety data from the U.S. and non-U.S. studies in order to "minimize the impact of potential differences in patient demographics and medical practice on the reporting and categorization of adverse events."

This review will follow the general format of the sponsor's integrated summary of safety. Using both separated and pooled datasets, the review of the safety of cerivastatin will address the overall incidence of adverse events relative to placebo and comparator lipid altering agents, as well as the relationship to dose and by demographic variables (race, age, sex). In addition, the discontinuations due to adverse events, the incidence of serious adverse events, and deaths will be reviewed. Treatment emergent malignancies and myocardial infarctions, issues of particular interest in lipid-altering trials, will be reviewed.

The main emphasis of the safety review will be on those adverse effects peculiar to the class of HMGRIs. Effects of cerivastatin on liver function and muscle enzymes as well as on testicular and adrenal function by dose and demography will be reviewed. As mentioned above, the ophthalmologic effects of cerivastatin will be reviewed. Finally, in part because of theoretical effects of statins on cellular energy metabolism via disruption of the electron transport chain (felt to contribute to the rare skeletal myotoxicity), any potential effects on cardiac muscle will be addressed in a brief review of the hemodynamic and electrocardiographic findings across treatment groups.

8.1 Exposure

The table below summarizes the overall exposure to cerivastatin, placebo, and active comparator agents in this NDA at the time of the original submission. As of the original submission, a total of 3860 people had received cerivastatin in clinical pharmacology and clinical studies across a

dosage range from 25 to 400 mcg. The numbers exposed in clinical studies in the table reflect patients valid for safety analysis. These are randomized patients who received at least one dose of study drug and for whom post-randomization data were collected.

Table 8.1.1. Total human exposures in NDA 20-740

	US Studies			Non-US Studies		
	Ceriva	Placebo	Active control	Ceriva	Placebo	Active control
Clinical	1171	247	186	2172	395	503
Clinical Pharm	289	88	0	228	65	0
Total	1460	335	186	2400	460	503

The numbers of patients valid for safety who were exposed to cerivastatin, placebo, and comparator drugs (lovastatin, simvastatin, and gemfibrozil) in the individual completed U.S. and non-U.S. clinical studies are summarized in the tables below. Patients receiving placebo in the short-term studies who went on to receive cerivastatin in long-term extensions (numbers in parentheses) are added to the short-term totals for total exposure. Those who continued on cerivastatin from short-term to long-term study are counted only in the short-term totals, though the numbers are included in the rows corresponding to the long-term extension studies.

Table 8.1.2. CER Exposure in Completed Studies (Patients Valid for Safety)

US	Number of Patients		
Study #	Ceriva 25-300µg	Placebo	Lova 40mg
D91-012	139	35	33
D91-016	273	46	n/a
D91-031	627	154	153
D92-010	24	12	n/a
Short-Term Totals	1,063	247	186
X91-031	463 (108)	n/a	117*
Total	1,171	247	186

Non-US	Number of Patients			
Study #	Ceriva 25-400µg	Placebo	Simva 5-40mg	Gemfibrozil 1200mg
0110	131	34	31	n/a
0120	780	192	186	n/a
0132	512	79	n/a	160
0139	36	18	n/a	n/a
0149	279	72	n/a	n/a
0126	259	n/a	126	n/a
Short-Term Totals	1,997	395	343	160
X0120	692 (175)	n/a	170*	n/a
X0126	94	n/a	59*	n/a
Total	2,172	395	343	160

The exposure by dose and duration of therapy in completed U.S. and non-U.S. studies is summarized in tables 8.3 and 8.4, respectively.

Table 8.1.3.
Number of CER-Treated Patients In US Studies by Treatment Duration and Dose
(Patients Valid for Safety)

Dose	1 month	6 months	12 months	24 months*
CER 25µg qd	33	0	0	0
CER 50µg qd	182	141	109	98
CER 100µg qd	186	139	98	91
CER 100µg bid	89	0	0	0
CER 200µg qd†	467	242	205	104

CER 300μg qd	172	135	104	98
TOTAL CER	1,129	657	516	391

* Range: 647 - 815 days

† Patients treated with PLA in D91-031 (6 months) were treated with CER 200μg in X91-031 (18 months). These patients are included in the CER 200μg 1, 6 and 12 month exposure columns.

Table 8.1.4.
Number of CER-Treated Patients In Non-US Fixed-Dose Studies by Treatment Duration and Dose
(Patients Valid for Safety)

Dose	1 month	3 months	12 months	24 months
CER 25μg qd†	359	292	217	78
CER 50μg qd	216	147	139	77
CER 100μg qd	382	311	147	95
CER 200μg qd	402	315	160	101
CER 300μg qd	327	164	0	0
CER 400μg qd	136	0	0	0
TOTAL CER	1,822	1,229	663	351

† Patients treated with PLA in 0120 (12 weeks) were treated with CER 25μg in X0120 (88 weeks). These patients are included in the CER 25μg 1, 3 and 12 month exposure columns.

Thus, the total number of patients with exposure ranging from 21 to 27 months was 742. The greatest exposure was at the 200 mcg dose, with 869 patients treated for one month and 205 patients treated for 21 to 27 months. The exposure at the highest dose proposed for marketing, 300 mcg, was 104 patients for 1 year, and 98 patients for from 21 to 27 months. An additional 33 patients (not included in the table because of the dose-titration study design) were treated in study 0126/X0126 (conducted in Canada) for two years. Based on the safety data that follows, this exposure appears to be adequate to assess the relative safety of the higher and lower doses of cerivastatin.

Overall demographics of the exposed population

Across the U.S and non-U.S. short term and long term trials, 55-60% of patients were male, 92-99% were caucasian, 0.1-6% were black (very few in the non-U.S. studies), and 75-80% were less than 65 years old.

8.2 Adverse events

The adverse event profile of cerivastatin was characterized by analysis of data from short-term and long-term U.S. and non-U.S. studies. The short-term fixed-dose studies were placebo-controlled and the data from them were thus analyzed for effects of age, gender, and race on the incidence of adverse events occurring more frequently in cerivastatin compared to placebo patients. In the long-term extensions, those patients randomized to placebo in the short term trials were switched to active treatment in the extensions. The long term studies allowed followup on the rates of selected adverse events that predominated in short-term treated cerivastatin patients relative to comparator agents.

In the U.S. studies the mean duration of treatment was similar for cerivastatin and placebo, and somewhat higher for lovastatin. The tables below summarize the adverse events occurring in >3% of patients in any treatment group in short term placebo-controlled studies. Table 8.2.1 contains the US data and table 8.2.2 contains the non-US data.

Table 8.2.1.
Adverse Events Occurring in ≥ 3% of Patients (in any treatment group) in Short-Term US Placebo-Controlled Studies
(Patients Valid for Safety)

	CER (n=1,063)	PLA (n=247)	LOV (n=186)
Mean Treatment Duration (weeks)	15	16	20
Any Event	68%	70%	81%
Body as a Whole			
Headache	11%	13%	12%
Flu Syndrome	7%	8%	12%
Accidental Injury	7%	7%	5%
Back Pain	5%	6%	8%
Abdominal Pain	4%	4%	8%
Asthenia	3%	3%	5%
Chest Pain	3%	3%	4%
Leg Pain†	2%	1%	3%

Digestive			
Dyspepsia	5%	5%	5%
Diarrhea†	5%	4%	8%
Flatulence	3%	4%	3%
Nausea	3%	3%	3%
Constipation	2%	2%	3%
Digestive Surgery	1%	4%	2%
Musculo-Skeletal			
Arthralgia†	7%	4%	8%
Myalgia†	2%	1%	4%
Nervous			
Dizziness	3%	4%	4%
Hypertonia	1%	1%	3%

† Shaded events occurred more frequently in CER versus PLA-treated patients.

Table 8.2.1. (continued)
Adverse Events Occurring in ≥ 3% of Patients (in any treatment group) in Short-Term
US Placebo-Controlled Studies
(Patients Valid for Safety)

	CER (n=1,063)	PLA (n=247)	LOV (n=186)
Mean Treatment Duration (weeks)	15	16	20
Respiratory			
Pharyngitis	13%	17%	20%
Rhinitis	11%	12%	16%
Sinusitis†	7%	6%	10%
Cough Increased†	3%	2%	5%

Bronchitis	2%	2%	3%
Skin and Appendages			
Rash	4%	6%	8%
Urogenital			
Urinary Tract Infection	1%	2%	3%
† Shaded events occurred more frequently in CER versus PLA-treated patients.			

The adverse events occurring in ≥ 3% of patients (in any treatment group) from the pooled Non-US short-term studies (0110, 0120, 0126, 0132, 0139, 0149) are shown in Table 8.2.2 below:

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Table 8.2.2.
Adverse Events Occurring in ≥ 3% of Patients (in any treatment group) in Short-Term Non-US Controlled Studies
(Patients Valid for Safety)

	CER (n=1,997)	PLA (n=395)	SIMVA (n=343)	GEM (n=160)
Mean Treatment Duration (weeks)	15	11	19	16
Any Event†	47%	44%	52%	47%
Body as a Whole				
Abdominal Pain	3%	3%	5%	4%
Asthenia	3%	3%	2%	1%
Back Pain†	3%	2%	2%	2%

Flu Syndrome†	5%	1%	9%	4%
Headache†	3%	2%	7%	2%
Infection†	3%	2%	2%	0%
Pain	1%	1%	3%	1%
Cardiovascular				
Angina Pectoris	2%	2%	1%	3%
Digestive				
Constipation	1%	2%	3%	3%
Diarrhea	3%	4%	3%	4%
Dyspepsia†	2%	1%	3%	1%
Flatulence	1%	2%	4%	2%
Gastrointestinal Disorder	1%	1%	1%	3%
Nausea	1%	2%	4%	2%
Vomiting	1%	1%	<1%	3%
Musculo-Skeletal				
Arthralgia	2%	2%	3%	1%
Myalgia†	2%	1%	4%	1%

† Shaded events occurred more frequently in CER versus PLA-treated patients.

Table 8.2.2. (continued)
Adverse Events Occurring in ≥ 3% of Patients (in any treatment group) in Short-Term Non-US Controlled Studies
(Patients Valid for Safety)

	CER (n=1,997)	PLA (n=395)	SIMVA (n=343)	GEM (n=160)
Mean Treatment Duration (weeks)	15	11	19	16
Respiratory				
Bronchitis†	2%	1%	1%	4%

Pharyngitis	1%	<1%	3%	1%
Upper Respiratory Infection	3%	3%	2%	4%
† Shaded events occurred more frequently in CER versus PLA-treated patients				

From the two tables above, one can see that the incidence of any event was significantly greater in the US than in the non-US studies, lending support to the rationale for analyzing the adverse event datasets separately. In both pools, the overall rates of adverse events were similar across treatment groups.

In the US pool, the most common adverse events (headache, flu syndrome, pharingitis, rhinitis, and sinusitis) occurred with similar frequency across treatment groups. For those adverse events that occurred more frequently in cerivastatin-treated versus placebo-treated patients (see shaded areas) the rates in the lovastatin treated patients always exceeded those in the cerivastatin treated patients. There were no statistically significant differences between treatment groups for any of the the events listed.

In the non-US pool, as was the case for all events, likewise the rates of any individual events were much lower than in the US pool. Again, for those events with rates higher in the cerivastatin than in the placebo patients, the rates in the comparator HMGRI (simvastatin) group were generally higher than in the cerivastatin group.

Adverse events by dose
When the adverse events occurring more frequently in the cerivastatin-treated versus placebo-treated patients were analyzed by dose in both the US and non-US pools, there was no relationship of adverse events rates to dose for any of the events considered.

Adverse events by gender
Analysis of the same events in the US and non-US pools by gender showed higher rates of any event in female placebo and cerivastatin-treated patients only in the US pool. Among individual events in that pool, only diarrhea occurred more frequently in the females treated with cerivastatin than among the males (6% vs. 3%). This is unlikely to be of clinical significance.

Adverse events by race
Analysis of these same selected events by race (black/white/other) showed an overall increased incidence of adverse events among blacks in both the US pool and non-US pool, though because of the small numbers of blacks enrolled in the trials (60 US, 8 non-US), no statistical analyses were performed. The most marked numerical differences were for arthralgia in the US pool (17% B vs 7% W) and for flu syndrome in the non-US pool (25% B vs. 4% W). This finding is unlikely

to be of clinical significance.

Adverse events by age
Analysis by age (<65 vs. ≥65) of the same events in the US and non-US pools showed that the incidence of any event was higher in old versus younger patients in the US studies but not in the non-US studies. For individual events, in the US pool, diarrhea and arthralgia occurred more frequently in both placebo and cerivastatin older patients and in the non-US pool, back pain occurred more frequently in older patients and in cerivastatin patients overall. These differences are unlikely to be of clinical significance.

Adverse events by gender and age
Analysis of the adverse events by gender and age in the two study pools showed that in the US patients, overall adverse events were increased in the female elderly, regardless of treatment group. For the individual events selected above, elderly females had the highest incidence of diarrhea and arthralgia, irrespective of treatment group. In the non-US studies, elderly females treated with cerivastatin had slightly higher rates of overall and individual adverse events than did other patients. The greatest numerical difference was for back pain (8% compared to 0-4% in the other groups).

In conclusion, analysis of the short term adverse event data by demographic groups reveals small effects of gender and age on adverse event rates, with elderly (>65 years) females reporting more overall adverse events than younger females or males as a group. For the most part, this same relationship existed within the placebo groups. No clinically significant findings arise from these analyses. Overall, in the short-term studies, cerivastatin was as well as or better tolerated than lovastatin and simvastatin. The profile of frequent adverse events was as is expected for a member of this class.

Adverse events in the long term extensions
The sponsor has analyzed and presented adverse event data by treatment group and dose from the three long term extension (US and non-US fixed dose, non-US dose-titration) and has listed rates for any event and for those individual events that occurred with greater frequency in the cerivastatin than in the placebo group in the corresponding pooled short-term studies. As a rule, the overall incidence of adverse events was higher for the long-term extension cohorts than for the short term pools, with increases up to 50% in rates of any event. This arises due to the increased period over which to develop and report symptoms, whether or not they are due to drug. The spectrum of adverse events did not change with increased duration of exposure. There were no dose-dependent differences in event rates in either the US or non-US long term extensions.

In the US study, the overall rates of leg pain and diarrhea were greater for the lovastatin-treated patients than for the combined cerivastatin-treated patients. The rates of myalgia and arthralgia were similar across treatments.

In the non-US extension, overall adverse event rates were again increased with no dose effect on rates of individual events and no differences for individual events between cerivastatin and simvastatin treated patients. In the extension of the dose-titration study (0126/X0126), the mean treatment duration was greater in the simvastatin group than in the cerivastatin group (14 vs. 11 months). The overall adverse event rate as well as the rates of flu syndrome, headache, and myalgia were thus also slightly greater in the simvastatin group than in the cerivastatin group.

Discontinuations due to adverse events

The discontinuation frequencies for the US short-term placebo controlled studies are summarized in the table below.

Table 8.2.3.
Discontinuation Frequencies for All US Short-Term Placebo-Controlled Studies (Patients Valid for Safety)

	CER (n=1,063)	PLA (n=247)	LOV (n=186)
Completed study	983 (92%)	226 (91%)	168 (90%)
Premature Termination† Due To:			
Adverse Events*	30 (3%)	7 (3%)	7 (4%)
Non Compliance	12 (1%)	1 (<1%)	2 (1%)
Consent Withdrawn	17 (2%)	5 (2%)	3 (2%)
Lost to Follow Up	2 (<1%)	2 (1%)	1 (1%)
Protocol Violation	11 (1%)	4 (2%)	2 (1%)
Other	8 (1%)	2 (1%)	3 (2%)

* includes deaths
† patients discontinued for only one reason

The data for the non-US pool (not shown) are similar, with overall completion rates between 89 and 93%, and 2 to 4% of discontinuations due to adverse events, including deaths.

The data for the long-term US extension are summarized in the table below and again show similar overall completion rates as well as rates of discontinuation due to adverse events across treatment groups.

Table 8.2.4.
Discontinuation Frequencies for US Long-Term Active-Controlled Study X91-031 (Patients Valid for Safety)

	CER (n=463)	PLA/CER 200μg* (n=108)	LOV (n=117)
Completed study	386 (83%)	89 (82%)	99 (85%)
Premature Termination† Due To:			
Adverse Events‡	34 (7%)	9 (8%)	9 (8%)
Non Compliance	4 (1%)	1 (1%)	2 (2%)
Consent Withdrawn	15 (3%)	5 (5%)	1 (1%)
Insufficient Therapeutic Effect	6 (1%)	1 (1%)	1 (1%)
Lost to Follow Up	6 (1%)	0 (0%)	1 (1%)
Protocol Violation	5 (1%)	2 (2%)	2 (2%)
Other	7 (2%)	1 (1%)	2 (2%)

* Patients received PLA in Study D91-031 and CER 200μg in Study X91-031.
† patients discontinued for only one reason
‡ includes deaths

In the non-US long term extensions, the completion rates were much lower due to the fact that study X0120 was structured as a two-extension study and many did not opt to continue into the second year of the extension. Again, however, the discontinuations due to adverse events were similar across groups (cerivastatin, placebo, simvastatin).

The analysis of discontinuations due to adverse events by dose in the fixed-dose short and long-term studies showed no dose-response and only small differences in rates between treatment

groups.

Types of adverse events leading to discontinuations

Of 1,171 CER-treated patients enrolled in the US short-term placebo-controlled studies and the US long-term active-controlled study X91-031 (including patients who received PLA in D91-031 and switched to CER 200µg in X91-031), 73 (6%) discontinued treatment due to 98 adverse events. Of the 247 PLA-treated patients enrolled, seven (3%) discontinued due to 12 events. Finally, of the 186 LOV-treated patients enrolled, 16 (9%) patients discontinued due to 23 events.

Of note, the mean duration of treatment was highest in the lovastatin group (15 months). The mean durations of treatment in the cerivastatin and placebo groups were 11 and 4 months, respectively. This may explain the increased frequency of certain events in the cerivastatin and lovastatin groups relative to placebo. The table below summarizes the data.

Table 8.2.5.
Discontinuations Due to Adverse Events by Type of Event in US Short-Term (D91-012, D91-016, D91-031 and D92-010) and Long-Term (X91-031) Studies (Patients Valid for Safety)

	CER* (n=1,171)	PLA (n=247)	LOV (n=186)
Mean Treatment Duration (months)	11	4	15
	Number of Events:‡		
Myocardial Infarction	4	0	2
Cerebrovascular	0	1	0
Other Cardiovascular/ Vascular	24	3	5
Digestive	11	1	6
LFT Abnormality	5	1	0
Joint/Muscle/Extremity	15	3	2
Cancer	10	0	3
Rash	5	0	1
CK Elevation	4	0	1
Depression	3	0	0
Amnesia	3	0	0

Urogenital	2	1	0
Accidental Injury	2	0	0
Headache	2	0	0
Cataract	2	0	0
Other†	6	2	3

* CER includes patients treated exclusively with CER and patients from the PLA group who received CER 200μg in the LTE.

† CER: pharyngitis, dizziness, sarcoidosis, insomnia, nervousness, asthenia;
PLA: sinusitis, amblyopia;
LOV: emotional lability, infection, parosmia

‡ Events are attributed to most specific category.

Of the adverse events causing discontinuation in CER-treated patients, most were categorized as 'other cardiovascular/vascular', joint/extremity and digestive causes. This pattern was also observed in PLA-treated patients. Digestive and 'other cardiovascular/vascular' causes were most common in LOV-treated patients.

The results of the non-US short and long term studies were similar.

Serious adverse events

Review of the serious adverse event experience in the US short and long term studies shows that, of the events felt to be potentially serious, most belonged to the category 'other cardiovascular/vascular' across all three treatment groups. Because the numbers of placebo and lovastatin treated patients and thus of serious adverse events were small relative to cerivastatin-treated patients and serious adverse events in that group, no statistical comparisons were made. Overall, however, the spectrum and frequency distribution of adverse events was similar across treatment groups. There were more accidental injuries in CER-treated patients. This likely reflects the higher patient-month exposure in the CER treatment group. There was no dose-response with respect to serious adverse events across the cerivastatin dosage range studied.

The data on serious adverse events from the non-US short and long-term studies were similar to those from the US studies.

Review of the narratives for the serious adverse events did not suggest any novel, clearly drug-related events that would distinguish cerivastatin in its potential toxicity from the class of HMGRIs.

Deaths

Of the 3,343 patients exposed to CER in clinical trials submitted to the original NDA for a mean treatment duration of 10 months, there were 9 (0.3%) deaths. Of these nine deaths, four occurred during the study (while on CER) and five occurred after the patient had withdrawn from or completed the study (no longer taking CER). Of the five patients who died after withdrawal from or completion of the study, 2 had experienced serious adverse events during the study which ultimately resulted in death. Of the 689 patients exposed to active control, there were 2 (0.3%) deaths during the study period.

The causes of death are summarized in the table below.

Table 8.2.6. NDA 20-740. Deaths

Patient #	Age	Race/Gender	Drug dose	Duration of treatment	Cause of death
3041	57	WM	Cer 300 mcg	84 days	cardiac arrest
4007	71	WM	Cer 50	544 days	MI/ventricular septal defect
13035	69	WF	Lova 40 mg	243 days	MI
6002	71	WM	Cer 100	3 days	cardiac arrest
75004	75	WF	Cer 25	113 days	MI 9d after completion of study
6014	58	WM	Cer 100	78 days	died during CABG 1 mos after withdrawal
1008	59	WM	Cer 100	106 days	MI/arrest
08/380	54	WM	Cer 300	56 days	sudden death 2d after completion
13006	54	WM	Cer 50	1 year	Ca of lung, PE, coronary occlusion
18001	70	WM	Cer 25	267	esoph ca after withdrawal
32005	45	WM	Simva 20 mg	___	presumed MI after randomization

Malignancies

In the US short and long-term studies, including 1,171 cerivastatin treated patients and 1054 patient years of exposure, most malignancies were of the skin and prostate. The number of events

per patient year were similar for CER (0.02), LOV (0.01) and PLA-treated (0.02) patients.

In the non-US studies, among 2,172 cerivastatin-treated patients with 1689 patient years of exposure, there were few cancers diagnosed and no predominance of type of malignancy. Event rates per patient years was 0.01 or less for all treatment groups.

Myocardial infarctions
The incidence of MI was similar across treatment groups for all patients exposed to treatment in studies submitted to the NDA. There was no dose-response with respect to MI incidence among the cerivastatin-treated patients.

8.3 Clinical laboratory safety
When the US short-term pooled clinical laboratory data were screened for abnormalities above the limits of normal, the differences between treatment groups in the rate of abnormalities in serum electrolytes and chemistries were restricted to glucose, CK, SGOT, SGPT. The rate of glucose elevations was greatest (35%) in the cerivastatin group compared to placebo and lovastatin (27% and 29%, respectively). The rates of any LFT and CK abnormalities (>ULN) were greater in the lovastatin group (27% and 27%, respectively) compared to the cerivastatin group (17%, 20%) and lowest in the placebo group (18%, 16%).

The rates of hematologic abnormalities, the most frequent of which were low WBC, hemoglobin, and hematocrit and elevated eosinophil counts and PTT, were similar across treatment groups.

Serum creatine kinase (CK)
In the US short term pool as well as in the US long term extension study, the incidence of any elevation to greater than the upper limit of normal for CK was similar in cerivastatin and comparator statin-treated patients and only slightly higher than in the placebo-treated patients. When patients were further categorized by degree of elevation above normal, likewise there was little difference in rates between treatment groups. There was no dose-response for incidence of CK elevations to any degree among cerivastatin-treated patients. The highest CK elevations were observed in the first 24 weeks of treatment in this cohort. The patient with the highest CK value (11,830) was a habitually sedentary 34 year old man who started weightlifting about 2 weeks after randomization to treatment with cerivastatin 200 mcg and complained of upper body soreness and stiffness from lifting weights. The relationship of the CK elevation to study medication is thus not clear.

In the US study pool, 2 of 1169 (0.2%) cerivastatin treated patients developed CK elevations to >10 times the ULN with muscle aching or weakness. This includes the patient described above. One of 245 placebo-treated patients and one of 185 lovastatin-treated patients developed CK elevations >10 times the ULN without symptoms.

At my request, the sponsor analyzed data pooled from all completed studies submitted to the NDA in June 1996 in order to assess further the effects of cerivastatin on muscle.

The table below summarizes the data from all patients with a post-randomization CK elevation to >10X ULN and/or who were discontinued due to CK elevations by dose of drug.

Table 8.3.1. CK elevation >10X ULN plus patients discontinued due to CK elevations									
cer 25 (n=438)	cer 50 (n=438)	cer 100 (n=602)	cer 100 BID (n=92)	cer 200 (n=972)	cer 300 (n=662)	cer 400 (n=139)	active statin (n=529)	gem 1200 (n=160)	placebo (n=642)
4 (0.9%)	2 (0.5%)	3 (0.5%)	0	3 (0.3%)	0	0	2 (0.4%)	0	2 (0.3%)

Among these patients, only 2 (both taking 200 mcg daily) experienced accompanying myalgia or myasthenia. One of these was the weight lifter described earlier.

In conclusion, clinically important CK elevations (>10X ULN) with or without symptoms were extremely rare in the studies reported in this NDA. The rates of CK elevations of lesser magnitude were similar across cerivastatin doses and other treatment groups. With respect to myotoxicity, cerivastatin appears safe in the doses studied.

Liver function testing

The sponsor analyzed separately the data for SGOT (AST) and SGPT (ALT) abnormalities in patients with normal or low values at baseline. The pattern that emerged follows. In the US long term studies, there was a dose response for the incidence of any elevation above normal up to 32-34% in the cohort treated for up to two years. Virtually all these elevations were to less than 2X the ULN. The rates of abnormalities by stepped categories of greater magnitude were between 0 and 1%. One patient treated with cerivastatin 200 mcg had an elevation > 10 X ULN. Most elevations occurred in the first 6 months of treatment. The table below summarizes the results from the US long term study for SGOT.

Table 8.3.2.
Percentage of Patients With A Normal or Low SGOT† at Baseline Who Developed An Increased SGOT
Through Two Years (and through 24-weeks in parentheses) During Double-Blind Therapy in Study D/X91-031 (Patients Valid for Safety)

	CER					
	50µg (n=149)	100µg (n=145)	200µg (n=151)	300µg (n=146)	LOV 40mg (n=145)	PLA/200µg[b] (n=139)
Mean Treatment Duration (months)	17	17	17	17	18	15
Any Elevation	24% (15%)	29% (19%)	34% (26%)	32% (23%)	37% (28%)	26% (21%)
> ULN to ≤ 2X ULN	23% (15%)	28% (19%)	33% (25%)	30% (21%)	36% (27%)	24% (19%)
>2X to ≤ 3X ULN	1% (1%)	1% (1%)	0% (0%)	1% (1%)	1% (1%)	1% (1%)
>3X ULN	1% (0%)	0% (0%)	1% (1%)	1% (1%)	0% (0%)	1% (1%)
Sustained High*	7% (4%)	11% (6%)	9% (7%)	13% (10%)	14% (8%)	6% (7%)
Maximum Value‡	277 U/L (n=158)	74 U/L (n=155)	279[a] U/L (n=159)	95[a] U/L (n=155)	65[a] U/L (n=153)	260[a] U/L (n=154)

† normal range: 8 to 22 U/L
* elevated at two consecutive visits or at the last visit
‡ this analysis includes all patients with evaluable data, therefore, the maximum value may occur in a patient who had an elevated SGOT at baseline
a occurred in Study D91-031 (the first 24 weeks of therapy)
b overall event rate includes both the PLA and CER 200µg treatment periods; event rate in parentheses represents 24-week treatment with PLA only

The range of normal for AST was 8-22 U/L in the US studies and 8-38 U/L in the non-US studies. This may explain the overall low rates (1-2%) and absence of a dose-response in the

incidence of any elevation in SGOT among patients in the non-US short term studies with normal SGOT at baseline. See the table below.

Table 8.3.3.
Percentage of Patients With A Normal or Low SGOT† at Baseline Who Developed An Elevated SGOT (Through Endpoint) During Double-Blind Therapy in the Fixed-Dose Pooled Short-Term Non-US Studies (0110, 0120, 0132, 0139 and 0149) (Patients Valid for Safety)

	CER								
	25µg qd (n=226)	50µg qd (n=226)	100µg qd (n=388)	200µg qd (n=410)	300µg qd (n=326)	400µg qd (n=137)	SIMVA 20mg qd (n=215)	GEM 600mg bid (n=160)	PLA (n=389)
Mean Treatment Duration (Weeks)	11	11	13	13	12	8	11	16	11
Any Elevation	2%	1%	2%	2%	2%	2%	3%	6%	2%
> ULN to ≤ 2X ULN	2%	<1%	2%	2%	2%	2%	3%	6%	2%
>2X to ≤ 3X ULN	<1%	<1%	<1%	0%	<1%	0%	0%	0%	0%
>3X ULN	0%	0%	<1%	<1%	0%	0%	0%	0%	<1%
Sustained High‡	1% (n=225)	0% (n=215)	1% (n=379)	1% (n=380)	1% (n=301)	0% (n=133)	<1% (n=208)	1% (n=153)	<1% (n=356)
Maximum Value*	92 U/L (n=228)	77 U/L (n=225)	230 U/L (n=389)	161 U/L (n=414)	113 U/L (n=331)	77 U/L (n=136)	61 U/L (n=217)	49 U/L (n=158)	118 U/L (n=389)

† Normal range: 8 to 38 U/L

* This analysis includes all patients with evaluable data, therefore, the maximum value may occur in a patient who had an elevated SGOT at baseline

‡ Elevated at two consecutive visits or last visit

The rates of any SGOT elevation and of elevations by degree above normal were similar between the cerivastatin patients and the control HMGRI patients (Lovastatin 40 in the US studies, Simvastatin 20 in the non-US studies). In the non-US studies, the highest rate of SGOT > ULN

was among the gemfibrozil treated patients, though they had the longest mean duration of treatment.

To further assess the effect of CER on serum transaminases (SGOT and SGPT), the percentage of patients in the US placebo-controlled short-term and active-controlled long-term studies (D91-012, D91-016, D92-010 and D/X91-031) who experienced increases in SGOT and/or SGPT ≥ 3X ULN at two or more occasions (not necessarily sequential) regardless of baseline status were evaluated for all patients with evaluable data. This occurred in four of 1,169 CER-treated patients (0.3%), one of 245 PLA-treated patients (0.4%) and one of 185 LOV-treated patients (0.5%). In three of the four CER-treated patients, the transaminase elevations occurred within five weeks after initiation of therapy, returned to normal after discontinuation of CER, were asymptomatic and not associated with cholestasis. The fourth patient received CER 50μg once daily for 24 weeks without problems. After entering the LTE, the patient was hospitalized for depression, received sertraline hydrochloride, desipramine hydrochloride, clonazepam and alprazolam and transaminase elevations ensued. CER was discontinued but the transaminase elevations persisted.

In summary, in the US study pool only, there was a slight dose-response for the incidence of any elevation of LFTs above normal, and the majority of these were less than 2X ULN. The overall incidence of clinically important LFT abnormalities (>3X ULN on 2 or more occasions) in the US pool was low, and the rates were similar for the cerivastatin treated and the placebo and lovastatin treated patients. In three of the four cerivastatin-treated patients with clinically important LFT elevations, these occurred within 5 weeks of the initiation of therapy. In the fourth patient, the transaminase elevations appear to have been due to other drugs or to drug-drug interactions occurring after 24 weeks of cerivastatin monotherapy not associated with adverse hepatic effects.

At my request, the sponsor analyzed pooled data from the completed studies submitted to the NDA in June 1996 in order to further assess the effects of cerivastatin on liver function.

Across the total cerivastatin-exposed population, the active-control statin, gemfibrozil, and placebo groups, there were no differences in the percentages of patients with LFT elevations to >3X ULN on two or more occasions (not necessarily sequential) and/or discontinuations due to transaminase elevations. The table that follows summarizes these data by dose of cerivastatin at which the event occurred.

Table 8.3.4. SGOT or SGPT elevation >3X ULN on 2 or more occasions (not necessarily sequential) plus patients discontinued due to LFT elevations

cer 25 (n=438)	cer 50 (n=438)	cer 100 (n=602)	cer 100 BID (n=92)	cer 200 (n=972)	cer 300 (n=662)	cer 400 (n=139)	active statin (n=529)	gem 1200 (n=160)	placebo (n=642)
0	2 (0.5%)	4 (0.7%)	0	2 (0.2%)	2 (0.3%)	0	2 (0.4)	0	1(0.2%)

No dose-response is apparent, and the overall rates are very low.

In conclusion, for the dosage range proposed for marketing, cerivastatin appears safe with respect to the induction of liver function abnormalities.

8.4 Glucose metabolism

While the percentage of patients in the US short term trials with elevations in fasting glucose was highest for the cerivastatin group, the same pattern did not emerge in the non-US short term pool. Here, the rates were significantly lower overall and similar between the treatment groups (10% cerivastatin, 9% placebo, 12% active control). The non-US pool was considerably larger (580 US cerivastatin-treated, 1498 non-US cerivastatin-treated) and the normal range for serum glucose extended to 110 mg/dL in contrast to 100 mg/dL in the US studies.

In the US pool, there was no dose response with regard to the incidence of glucose abnormalities overall. Furthermore, most elevations in the total US treatment experience, short and long term (~80%) were less the 10% above normal. Finally, across treatment groups in the US, in the majority (85% cerivastatin, 90% placebo, 71% lovastatin) of patients with glucose elevations, levels returned to normal on subsequent determinations.

In summary, perhaps explained by the higher upper limit of normal in the non-US studies, the relatively high rate of observed minor elevations in serum glucose in the US short-term cohort (across all treatment groups) was not replicated in the results with the non-US pool. Furthermore, these were, in the majority of cases, single isolated abnormalities, and do not suggest a real safety issue for cerivastatin.

8.5 Endocrine function

There was no evident effect of cerivastatin on thyroid or adrenal function as measured by serum thyroxine, TSH and cortisol. The review of effects on stimulated adrenal and gonadal function will be covered in a different section.

8.6 Cardiac/hemodynamic function

Across the US and non-US study pools, there were no clinically significant changes in heart rate, systolic or diastolic blood pressure at any dose of cerivastatin nor in the active control or placebo treated patients.

Eletrocardiographic abnormalities

There was no apparent effect of cerivastatin on the overall incidence or the distribution of EKG abnormalities by specific type.

8.7 Ophthalmologic effects

As mentioned earlier, in preclinical development, lovastatin treatment was associated with an increased incidence of cataracts in dogs. For this reason, FDA has required ophthalmologic evaluations of subsets of patients treated in controlled trials during development of the other

HMGRIs.

In study D/X91-031, the US pivotal dose-ranging study and its long term extension, ophthalmologic examinations were performed at baseline, after 24 weeks, and after 24 months of double-blind therapy (or at the time of discontinuation). A similar analysis of lenticular changes was performed in the non-US fixed-dose study 0120/X0120, with exams performed at baseline, after 12 weks, 12 months and after 100 weeks of double-blind therapy (or at the time of discontinuation).

There was no increase in the incidence of clinically significant new ophthalmologic findings across the cerivastatin dosage range and the rates were similar across treatments. When the US and non-US short and long term pools were analyzed for incidence of treatment-emergent lens opacities, again there was no difference in incidence across treatment groups or across the dosage range of cerivastatin.

In conclusion, at the doses studied and over the duration of exposure in the above trials, cerivastatin had no adverse effects on the eye.

8.8 Effects on adrenal and gonadal function

As discussed above, the marketed HMGRIs have no clinically significant effects on adrenal or gonadal function. The steroid-producing tissues use as substrate cholesterol derived from LDL taken up by LDL-receptors as well as HDL, from which cholesterol ester is hydolyzed after binding to a "docking" receptor. Nevertherless, the theoretical possibility still exists that with sufficient systemic exposure, either tonic or stimulated adrenal or testicular function might be affected. For these reasons, the sponsor carried out and has presented the results of a 6-month, placebo- and active-controlled, double-blind study of the effects of cerivastatin on semen production and adrenal and gonadal function in male patients with hypercholsterolemia.

Study design

Males, aged 20-60 years, with primary hypercholesterolemia and CLDL-C >140 with TG < 350 were eligible if they were willing and able to provide semem specimens. After a placebo, diet and drug washout run-in period, patients were randomized (1:1:1) to receive in double-blind fashion, either placebo, cerivastatin 300 mcg, or lovastatin 40 mg for at treatment period of 24 weeks.

Exclusion criteria included history of testicular tortion or other testicular abnormality, active atherosclerotic vascular disease, recent MI or revascularization procedure. In addition, patients were excluded with diabetes mellitus, renal disease, hyperprolactinemia, thyroid abnormality, or significant cataracts.

Endpoints included change from baseline to 24 weeks in LDL-C, sperm count, cortrosyn stimulated cortisol production, hCG-stimulated testosterone production, and 24-hour urinary hormone levels.

NSAIDs, ACE inhibitors, beta-blockers, calcium channel blockers, and diuretics, though relatively few patients received these concomitant medications compared to the numbers receiving cerivastatin alone. Suffice it to say, that for these medications likely to be commonly prescribed in patients receiving cerivastatin, no gross interactions leading to adverse events were evident. With regard to labeling, however, there are insufficient data to support a statement as to the safety of cerivastatin in combination with the above classes of drugs.

8.10 Four-month safety update

This was submitted on October 25, 1996
The four-month safety update includes the full safety experience from a single additional US study completed since the submission of the original NDA in June 1996. The update was submitted prior to the completion of study D94-021 (adrenal/reproductive) reviewed above. In addition, for the ongoing studies in the US and abroad, it includes the patient narratives (and the corresponding CRFs) for discontinuations due to adverse events, serious adverse events, and deaths occurring through June 28, 1996. This information will be reviewed and summarized and the information on total exposure to cerivastatin across the dosage range will be updated (not including the patients from D94-021).

In addition, the submission contains brief descriptions of ongoing US and non-US studies, which will be summarized here in order to catalogue the type of clinical information to be expected in the ongoing development of cerivastatin.

8.10.1 Completed and ongoing studies

Completed
Study Y91-031 is the second extension of the US pivotal trial D91-031. The original trial was 24 weeks in duration, and X91-031 extended the treatment across the dosage range to 2 years. In the current extension, all cerivastatin patients not already on 300 mcg/day were switched to that dose for an additional treatment and monitoring period of 6 months, thus significantly increasing the exposure to cerivastatin 300 mcg. The revised total exposures in the NDA will be summarized in a table later in this section.

Ongoing studies
As mentioned above, these will be described in brief in order to clarify the ongoing approach to the development of cerivastatin and to permit this review to serve as a reference on the planned studies with this new drug.

Z91-031 is the third extension of D91-031. Again, the original 6-months dose-ranging study was extended (X91-031) to 2 years for which the original placebo patients were switched to cerivastatin 200. For the second extension (Y91-031), all patients not on cerivastatin 300 mcg or lovastatin were switched to cerivastatin 300. Z91-031 continues treatment through December

1996 and calls for increasing all cerivastatin patients to 400 mcg daily by May 1996. The enrollment is approximately 481 patients (~400 on cerivastatin).

Study D96-007 is a 12-week (treatment period), parallel group, randomized, double-blind study that will compare the safety and efficacy of cerivastatin 200 and 300 to that of fluvastatin 20 mg and 40 mg in patients with hypercholesterolemia.

Study D96-008 is a randomized, double-blind, multi-center, parallel group, two-part study. It is intended to evaluate the safety and efficacy of cerivastatin 400 mcg compared to cerivastatin 300 and placebo over the first 8 weeks of the trial after which the placebo patients will be switched to fluvastatin 40 mg, permitting comparison of the safety and efficacy of cerivastatin at 300 and 400 mcg daily to that of fluvastatin 40 mg. The total duration of the trial will be 18 months. The study population is men and women 18-75 years with primary hypercholesterolemia.

Study X0132 is an extension of non-US pivotal dose-ranging study 0132. The original study, 16-weeks in duration, compared safety and efficacy of cerivastatin across the dosage range (110, 200, 300 mcg) to that of gemfibrozil 600 mg BID and placebo. The first extension was 36 weeks bringing the total duration of followup to 1 year, with the placebo patients switched to cerivastatin. Another extension brings the duration of treatment to 2 years during which all cerivastatin patients now dosed at 300 mcg daily.

Study X0139 is an extension of the South African study in FH heterozygotes. The study is ultimately to be extended to 2 years with patients on cerivastatin up to 300 mcg daily.

Ten studies currently ongoing in Japan (0127, 0130, 0131, 0140, 0141, 0143, 0144, 1045, 0146, 0147). Over 1000 patients have been enrolled as of the 4-month safety update. Individual studies examine the effects of cerivastatin across four doses on the composition of biliary lipids, investigate the efficacy of cerivastatin plus cholestyramine and probucol in FH, examine the efficacy of cerivastatin in comparison to pravastatin, the effects of cerivastatin on steroid hormone metabolism, on hemostasis, on serum lipids and glucose tolerance in diabetics, and compare safety and efficacy in the young versus the elderly.

Study 0156 is a study in China of 4-months' duration examing the safety and efficacy of cerivastatin 100, 200, 300 mcg compared to placebo in patients with hypercholesterolemia.

There are 4 ongoing clinical pharmacology studies, all of interest.

Study 0157 evaluates the interaction of cerivastatin 300 mcg with erythromycin. Two doses of cerivastatin will be given.

Study 0122 is a Japanese study of 4 weeks duration in 42 subjects to evaluate the cerivastatin dosage range of 25, 50, 100, and 200 mcg.

Study D96-012 is a multiple dose pharmacokinetic and safety study evaluating the interaction of cerivastatin 300 and erythromycin 500 BID given for 10 days.

Study D96-019 investigates multiple dose pharmacokinetics of cerivastatin 300 mcg daily in patients with mild to severe renal disease over 7 days of treatment.

8.10.2 Exposure

As a consequence of the completion of study Y91-031 since the submission of the NDA, the table for exposure to cerivastatin in US studies has been updated. The table is identical to table 8.3 in this section with the addition of the bolded numbers. All the patients enumerated in the 30-month column were treated with cerivastatin 300 mcg up to that timepoint, with those in the 50, 100, and 200 mcg rows having been switched to 300 mcg after the 24-month timepoint. In addition, more 200 mcg-treated patients are listed in the 24-months exposure column, reflecting patients originally randomized to placebo and switched to cerivastatin 200 having passed through the 24-month exposure timepoint.

Table 8.10.2.1.
Number of CER-Treated Patients In US Studies by Treatment Duration and Dose
(Patients Valid for Safety)

Dose	1 month	6 months	12 months	24 months	30 months *
CER 25µg qd	33	0	0	0	**0**
CER 50µg qd	182	141	109	98	**82**
CER 100µg qd	186	139	98	91	**77**
CER 100µg bid	89	0	0	0	**0**
CER 200µg qd†	467	242	205	**180**	**86**
CER 300µg qd	172	135	104	98	**82**
TOTAL CER	1,129	657	516	391	**329**

* This timepoint refers to total cerivasatin exposure duration. All patients in this column were switched from their respective cerivastatin dose to cerivastatin 300 daily from month 24 to 30; range 814-983 days

† Patients treated with PLA in D91-031 (6 months) were treated with CER 200µg in X91-031 (18 months). These patients are included in the CER 200µg 1,6, 12, and 24 month exposure columns.

In a effort to increase the exposure to 300 mcg in the non-US pool, the completion of study X0132 was reported in the 4-month safety update, though the final report has not been submitted.

While no changes have been made to the table below summarizing the non-US fixed-dose exposure, in that study, the sponsor states that more than 100 patients received cerivastatin 300 for one year, increasing the overall exposure (US and non-US, see table above) at this dose to greater than 200 patients for one year. The deaths, serious adverse events, and discontinuations due to adverse events for this study are included in the safety update and are unremarkable in number or specific nature.

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Table 8.10.2.2.
Number of CER-Treated Patients In Non-US Fixed-Dose Studies by Treatment Duration and Dose
(Patients Valid for Safety)

Dose	1 month	3 months	12 months	24 months
CER 25µg qd†	359	292	217	78
CER 50µg qd	216	147	139	77
CER 100µg qd	382	311	147	95
CER 200µg qd	402	315	160	101
CER 300µg qd	327	164	0	0
CER 400µg qd	136	0	0	0
TOTAL CER	1,822	1,229	663	351

† Patients treated with PLA in 0120 (12 weeks) were treated with CER 25µg in X0120 (88 weeks). These patients are included in the CER 25µg 1, 3 and 12 month exposure columns.

8.10.3 Adverse events In Y91-031

In study Y91-031, there were no changes in the spectrum or frequency of adverse events from the earlier experience, and no substantive differences between cerivastatin and lovastatin groups. Furthermore, there were no major differences in the spectrum or frequency of adverse events between those patients who were up-titrated to cerivastatin 300 mcg for the last 6 months and those who received 300 mcg for the entire treatment period. For those adverse events occurring more frequently among cerivastatin patients than placebo patients in the original pooled short term US studies, including diarrhea, arthralgia and myalgia, the rates were similarly low (0-4%) across lovastatin, cerivastatin 300 up-titrated, and cerivastatin 300 full-treatment-course groups.

Similarly, the discontinuations due to adverse events were similar in frequency across treatment groups, with no specific events remarkable as being clearly due to drug.

8.10.4 Laboratory safety

CK elevations

The experience in study Y91-031 with regard to CK elevations was similar to the previous experience, with similarly low rates of any elevation across treatment groups (2-7%) and all but one of the elevations being to $\leq$ 3X ULN. This elevation was <5X ULN.

SGOT/SGPT elevations

No patient had an elevation of SGOT to > 3X ULN and one patients had SGPT > 3X ULN. The rates of minor ($\leq$3 X ULN) LFT elevations were similar across treatment groups and between the up-titrated 300 mcg cervastatin patients and those on 300 mcg for the entire treatment period.

8.11

Safety update, dated May 14, 1997

The final safety update, required within 90 days of the final action due date for the NDA, was submitted on May 16, 1997. This includes data from three trials completed since the submission of the NDA (two of which were completed after the submission of the 4-month safety update).

This brief summary will update the total exposures in the US and non-US pools by dose and duration. With regard to adverse events, deaths, and laboratory abnormalities, no significant findings emerge that change the overall conclusions regarding the safety of cerivastatin based on the materials reviewed earlier.

The exposure in US studies shown in the table below is changed only by the addition of patients from study D94-021 (the 6-month study of effects on adrenal and gonadal function). These patients are added to the 1-month and 6-month totals for the 300 mcg group. As noted above, after two years of CER 50, 100 and 200µg once daily therapy in D/X91-031, patients were

switched to CER 300µg once daily in Study Y91-031. Patients receiving CER 300µg once daily were treated for an additional six months. Thus, all the patients in the 30-month column received 300 mcg, those in the 50, 100, and 200 mcg groups for only the last 6 months of therapy. Also, the number of patients receiving CER 200µg once daily for 24 months increased from 104 patients to 180 patients. This number reflects patients originally randomized to placebo in D91-031 who were switched to CER 200µg and then to CER 300µg passing through the overall 24 month exposure timepoint.

Table 8.11.1.
Number of CER-Treated Patients In Completed US Studies by Treatment Duration and Dose (Patients Valid for Safety)

Dose	1 month	6 months	12 months	24 months	**30 months*‡** (CER 300µg)
CER 25µg qd	33	0	0	0	**0**
CER 50µg qd	182	141	109	98	**82**
CER 100µg qd	186	139	98	91	**77**
CER 100µg bid	89	0	0	0	**0**
CER 200µg qd†	467	242	205	**180**	**86**
CER 300µg qd	**210**	**168**	104	98	**82**
TOTAL CER	**1,167**	**690**	516	**467**	**327**

* This timepoint refers to total CER exposure duration. All patients in this column were switched from their respective CER dose to CER 300µg once daily from months 24 to 30.

‡ range: 814 to 983 days

† Patients treated with PLA in D91-031 (6 months) were treated with CER 200µg in X91-031 (18 months) and CER 300µg in Y91-031 (6 months). These patients are included in the CER 200µg 1, 6, 12 and 24 month exposure columns, however the last six months of the total two year exposure was exposure to CER 300µg.

The updated non-US exposure is summarized in the next table. With the completion of study X0132, the one-year exposure to cerivastatin 100, 200, and 300 is increased. Also in that study, patients originally randomized to placebo were switched to cerivastatin 100 mcg are included in the updated figures for the 1-month and 3-months exposures.

Table 8.11.2.
Number of CER-Treated Patients In Non-US Fixed-Dose Studies by Treatment Duration and Dose (Patients Valid for Safety)

Dose	1 month	3 months	12 months	24 months
CER 25μg qd†	359	292	217	78
CER 50μg qd	216	147	139	77
CER 100μg qd‡	**449**	**372**	**280**	95
CER 200μg qd	402	315	**290**	101
CER 300μg qd	327	164	**140**	0
CER 400μg qd	136	0	0	0
TOTAL CER	**1,889**	**1,290**	**1,066**	351

† Patients treated with PLA in Study 0120 (12 weeks) were treated with CER 25μg in X0120 (88 weeks). These patients are included in the CER 25μg 1, 3 and 12 month exposure columns.

‡ Patients treated with PLA in Study 0132 (16 weeks) were treated with CER 100μg in X0132 (36 weeks). These patients are included in the CER 100μg 1 and 3 month exposure columns.

8.12 Conclusion with regard to the safety of cerivastatin 50-300 mcg daily
Adequacy of exposure in this NDA

The overall exposure to cerivastatin approaches 3500 in US and non-US short and long-term clinical studies. With the completion of the latest US long term extension out to 30 months and the completion of study X0132 (non-US) out to one year, the exposure in the US and abroad to cerivastatin 300 mcg is greater than 550 patients for at least 6 months, ~250 patients for at least one year, ~100 patients for at least 2 years, and ~80 patients for 30 months.

At the doses proposed for marketing (50-300 mcg daily), the drug appears safe with respect to common adverse reactions associated with statin therapy, and with respect to laboratory abnormalities notably hepatic enzyme elevations and CK elevations. Specifically, the overall incidence of clinically important LFT or CK elevations and/or discontinuation due to same was very low, not different than that seen in the active control or placebo groups, with no apparent dose response among the cerivastatin-treated patients.

There were no effects of cerivastatin on the eye, on adrenal or reproductive function, and no interaction evident with drugs used commonly among patients likely to be treated with cerivastatin.

Finally, no novel adverse events attributed to cerivastatin were noted, suggesting that the adverse event profile of this drug is similar to that of other members of the class.

In short, cerivastatin appears safe across the dosage range of 50-300 mcg daily.

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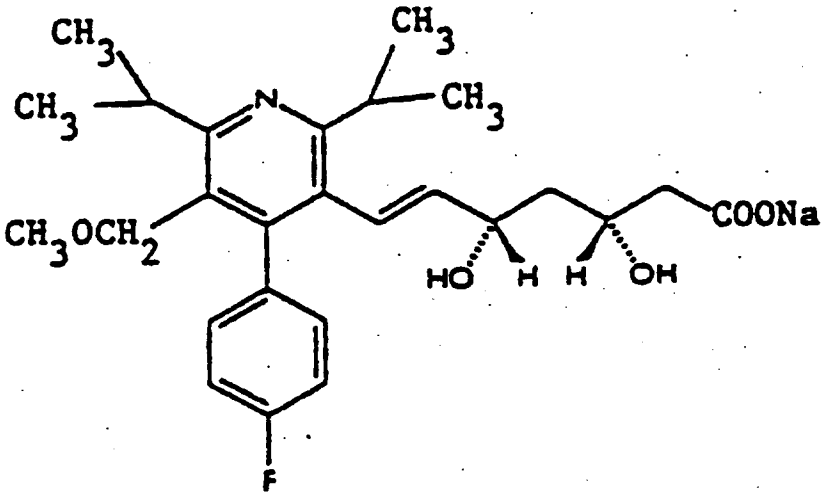
Section 9
Labeling review

The text and tables of the proposed package insert for cerivastatin are reproduced below. Suggested changes will be made using either redline (insertions) or ~~strikeout~~ (deletions). Comments where needed are made in *italics*.

BAYCOL™
(cerivastatin sodium tablets)

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 inclusion of broad summary statements addressing certain demonstrated clinical benefits of lipid lowering, of summary data from the LRC-CPPT using cholestyramine, and of references to the 4S and WOSCOPS trials and their results in the label for cerivastatin should be deleted. Such information is not essential for the safe and effective use of the drug. Furthermore, the inclusion of this information implies effectiveness of cerivastatin not demonstrated in well-controlled trials using the drug. At this point in time, there is sufficient general knowledge as to the presumed benefits of cholesterol lowering such that no explicit rationale for treatment need be provided in labeling. Finally, the inclusion in the labels of all the lipid lowering agents of the NCEP guidelines itself provides the relevant information necessary for the identification of the appropriate treatment populations for these drugs and for the determination of individualized treatment goals. These guidelines, in addition to information in each label pertaining specifically to the labeled drug, provide sufficient information for the safe and effective use of each agent.

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/Metabolism

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 AUC and C_{max} is in the 20% to 40% range.[8,9,10,11,12] The relative bioavailability of cerivastatin sodium tablets is equivalent to that of a solution of cerivastatin sodium.[7] No unchanged cerivastatin is excreted in feces[13] and absorption is presumed to be complete, with a fraction of the dose (~40%) most likely metabolized prior to reaching the systemic circulation. 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] 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]

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 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. 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 of ^{14}C-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]

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.

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]

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 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.

Caution should be exercised when BAYCOL™ (cerivastatin sodium tablets) is administered to patients with a history of liver disease or heavy alcohol ingestion (See WARNINGS).

Clinical Studies

BAYCOL™ (cerivastatin sodium tablets) has been studied in controlled trials in North America , Europe, Israel, and South Africa and has been shown to be effective in reducing plasma total cholesterol (Total-C) and LDL cholesterol (LDL-C) in heterozygous familial and non-familial forms of hypercholesterolemia and in mixed hyperlipidemia.[5]

Over 2,800 patients with Type IIa and IIb hypercholesterolemia were treated in trials of 4 to 104 weeks duration.[24] In a 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. Significant reductions in mean total-C and LDL-C were evident after one week. The mean responses reported in Table 1 occurred after 4 weeks and were maintained for the duration of the trial.

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					
BAYCOL™					
0.05 mg qd					
0.1 mg qd					
0.2 mg qd					
0.3 mg qd					

The table below shows the results for the intent-to-treat population. In addition, the mean responses in apo B should be included in the table.

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

The summary statement regarding the optimal time of dosing of cerivastatin is sufficient. The inclusion of the table from the study is potentially misleading in that the apparent efficacy of the drug exceeds that observed in the pivotal US study. The dose-scheduling study was not a pivotal trial, was of only 28 days' duration, and was significantly smaller than study D91-031.

INDICATIONS AND USAGE

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

Before considering therapy with lipid-altering agents, secondary causes of hypercholesterolemia, e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism, should be excluded and a lipid profile performed to measure Total-C, HDL-C, and triglycerides (TG). For patients with TG less than 400 mg/dl, LDL-C can be estimated using the following equation:

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

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).

*** In CHD patients with LDL-C levels 100-129 mg/dL, the physician should exercise clinical judgement 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 is the LDL-C level is ≥ 130 mg/dL (NCEP-ATP II).

These statements are included in ATP-II and are appropriate for the labeling of agents that act to lower total and LDL-C.

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 redlined section should be bolded.)*

The risk of myopathy during treatment with other HMG-CoA reductase

inhibitors is increased with concurrent administration of cyclosporine, fibirc acid derivatives, erythromycin, azole antifungals, or lipid lowering doses of niacin

Uncomplicated myalgia has been observed infrequently in patients treated with cerivastatin sodium at rates that could not be distinguished from placebo.[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, Fibric acid derivatives, Niacin (Nicotinic Acid), Erythromycin, Azole antifungals: See WARNINGS: Skeletal Muscle.

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 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 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 digoxint 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. This study also showed that digoxin did not alter the pharmacokinetics of cerivastatin.

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.

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

clinically significant adverse interactions.[40]

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. *The sponsor has completed and submitted the results of a study of the effects of cerivastatin on male reproductive function. The results and conclusions should be summarized here.*

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 or activity of endogenous steroid hormones.

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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
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]

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.[51] 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 pregancy and was discontinued at some point in the first trimester when pregnancy was indentified. 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 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 that 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]

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]

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Clinical Adverse Experiences

Adverse experiences occurring with a frequency >2%, regardless of causality assessment, 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~~ fibric acid derivatives, erythromycin, azole antifungals, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended (*See* WARNINGS: *Skeletal Muscle.*)

OVERDOSAGE

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

Like most other drugs of this class, the dialyzability of cerivastatin sodium and its metabolites in humans is not known.

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.

Dosages should be individualized according to the recommended goal of therapy (see NCEP Guidelines) and the patient's response.

Plasma lipid levels should be analyzed about 4 weeks after initiation and/or titration of cerivastatin, and the dosage adjusted according 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 binding resin.[61] 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

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 of renal disease should be started at the low end of the recommended dosing range and closely monitored.[19]

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.

Section 10
Summary and conclusions

Cerivastatin sodium is a purely synthetic HMG-CoA reductase inhibitor. It is administered as the salt of the hydroxy acid (active) form. It is a highly potent inhibitor of HMG-CoA reductase, approximately 100 times more potent than lovastatin.

This NDA contains data from extensive preclinical pharmacological and toxicologial investigations in animals, human pharmacokinetic studies, and human clinical studies of the safety and efficacy of chronic administration of cerivastatin. In addition, limited drug interaction studies and a study of the effect of cerivastatin on male adrenal and reproductive function have been undertaken and the results submitted. A study of the interaction of cerivastatin with erythromycin is planned.

No novel toxic reactions were observed in animals. In studies in mice, the carcinogenic potential of cerivastatin in the liver was similar to that of other HMGRIs with respect to the relationship of the mouse systemic exposures to human exposures at the maximum recommended dose. Furthermore, what is likely more reflective of hepatic exposure in these animal studies, the dose per body weight, far exceeds the proposed human doses. The spectrum of hepatic adenomas and carcinomas in animals was the same as that seen with other HMGRIs.

The pharmacokinetic studies reveal good oral bioavailability (60% absolute, and linear pharmacokinetics over a dosage range from 50 to 400 mcg. The elimination half-life No drug accumulation was observed with chronic once daily dosing.

The proposed dosage range for cerivastatin is 50 to 300 mcg once daily in the evening. The absolute efficacy of the drug at these doses in LDL-C lowering is limited relative to other marketed statins. Data from the pivotal efficacy studies showed mean LDL-C lowering in response to 300 mcg daily of approximately 30%. In addition to inducing the expected lesser effect on total-C that parallels the dose-related effect on LDL-C, cerivastatin, like the other members of the class, effected non-dose-related mean increases in HDL-C and mean reductions in TG in patients with primary hypercholesterolemia or mixed dyslipidemia (with elevations in VLDL). The mean reductions in TG were, at the higher doses of drug, statistically significantly different from placebo.

Cerivastatin was shown effective in FH heterozygotes but was not studied in FH homozygotes.

The exposure to cerivastatin in controlled clinical trials in this development program was substantial, with nearly 3500 patients treated across the dosage range. The exposure to 300 mcg daily was greater than 550 patients for at least 6 months, ~250 patients for at least

one year, ~100 patients for at least 2 years, and ~80 patients for 30 months. Fewer than 10% of patients studied in both the US and abroad were non-Caucasian. Multiple studies in Japan are ongoing. Women were well represented, constituting approximately 50% of the patients studied. Pediatric patients were not studied. Finally, in an 8-week study comparing cerivastatin 400 mcg to cerivastatin 300 mcg (~140 patients each) and to placebo (~70 patients), the doses of cerivastatin were equally well tolerated.

No unexpected adverse events attributed to cerivastatin were observed in the clinical trials. In general, the drug was very well tolerated. Few adverse events occurred more frequently among cerivastatin than placebo patients, and for those events, the rates among active control statin-treated patients were generally higher than among the cerivastatin patients. These included diarrhea, arthralgia, myalgia, sinusitis, and increased cough. There were no clear effects on adverse event rates of dose, gender, or age.

There were no dose related effects on the incidence of clinically important LFT abnormalities or on the rate of discontinuation due to transaminase elevations. Such events were rare overall (<1%). Similarly, there were no dose related effects on the incidence of significant CK elevations or on the rate of discontinuation due to CK elevations. Again, these events were rare (<1%).

With regard to labeling, I have recommended that the efficacy data presented be based on analysis of data from the intent-to-treat populations in the interest of consistency with labeling of other lipid altering agents.

The other major addition to the proposed label is the inclusion in the Pregnancy section of information gleaned from the recently published followup of patients inadvertently exposed to lovastatin and simvastatin, for the most part in the early first trimester of pregnancy. This review found no increase in the incidence of fetal anomalies, miscarriages, or stillbirths relative to the expected rates in the general population. The use of HMGRIs in pregnancy is still contraindicated. This information is included in labeling to inform physicians and patients of recent data speaking to the risks to the fetus of inadvertent exposure to these agents *in utero*.

Conclusions

Cerivastatin sodium, a new HMG-CoA reductase inhibitor appears safe and effective as proposed for use in patients with primary hypercholesterolemia and mixed dyslipidemia at doses from 50 to 300 mcg once daily. This conclusion is based on data from extensive preclinical studies and on safety and efficacy data from a large exposure in human clinical trials, up to 30 months at the highest dose (300 mcg) proposed for marketing.

Section 11
Recommendations
Based on the materials reviewed and pending agreement on final labeling, BAYCOL (cerivastatin sodium) tablets should be approved for marketing as proposed in NDA 20-740.

David G. Orloff, M.D.
Medical Officer/Team Leader
DMEDP/CDER/FDA

5-29-97

concur: Dr. Sobel

cc:
NDA Arch 20-740
HFD-510

6/4/97

APPEARS THIS WAY
ON ORIGINAL

All safety update information have been included in Medical Officer Review as of May 29, 1997

APPEARS THIS WAY
ON ORIGINAL