

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020740/S002

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

MAY - 3 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-740
Baycol™ 0.4 mg
Cerivastatin Sodium Tablets

SUBMISSION DATE: July 16, 1998

Bayer Corporation

REVIEWER: Hae-Young Ahn, Ph.D.

SUBMISSION TYPE: Efficacy Supplement: 0.4 mg Dose

SYNOPSIS: Cerivastatin is an HMG-CoA reductase inhibitor, currently marketed as 0.2 mg and 0.3 mg tablets. The current submission extends the dose range to 0.4 mg in order to achieve greater efficacy. In order to support the dose increase, one pharmacokinetic study (study 159, a dose proportionality and bioequivalence study) and one safety/tolerability study (study D97-001), which also collected pharmacokinetic/pharmacodynamic information, were submitted in Human PK section. In addition, in a phase 3 trial, a pharmacokinetic study (study D96-001) was conducted in a subpopulation.

The approved package insert states that

“The recommended starting dose is 0.3 mg once daily in the evening. Cerivastatin sodium may be taken with or without food. The recommended starting dose in patients with significant renal impairment (creatinine clearance ≤ 60 mL/min/1.73 m²) is 0.2 mg once daily in the evening”.

The proposed package insert states that



The following information was obtained from a bio-review of the original submission:

The mean absolute bioavailability of cerivastatin following 0.2 mg oral dose given as 2 x 0.1 mg is 60%. Cerivastatin exhibits linear kinetics over the dose range of 0.05 to 0.4 mg daily. No drug accumulation has been observed with once daily dosing. The pharmacokinetics is similar under fed and fasted conditions. Cerivastatin is metabolized by CYP3A4 to form three active metabolites; M1, M23 and M24.

Steady state plasma concentrations of cerivastatin are similar in healthy volunteers (Clcr >90 mL/min/1.73 m²) and in patients with mild renal impairment (Clcr 90 - 60 mL/min/1.73 m²). In patients with moderate (Clcr 31-60 mL/min/1.73 m²) or severe (Clcr ≤ 30 mL/min/1.73 m²) renal impairment, AUC is up to 60% higher, Cmax up to 23%, t_{1/2} up to 47% longer compared to subjects with normal renal function.

SUMMARY:

Dose Proportionality:

Single dose: The pharmacokinetic study (study 159) was a randomized, 3 way crossover study where BAY w 6228 was administered as a single oral dose of one 200 µg or 400 µg tablet or two 200 µg tablets in 24 healthy male volunteers (one week washout phase). The study drug was administered two hours after dinner at 7 pm and pharmacokinetic profiles were taken over the 24 hour following administration.

Plasma and urine samples are assayed for cerivastatin and its metabolites M1, M23, and M24 (only urine samples) using validated [REDACTED] assays.

Table 1. Pharmacokinetic parameters of cerivastatin following administration of different tablets and doses (geometric mean, CV)

	1 x 0.2 mg	2 x 0.2 mg	1 x 0.4 mg
AUC (µg*hr/L)	9.57 (46%)	18.1 (45%)	17.6 (44%)
C _{max} (µg/L)	1.5 (47%)	3.0 (46%)	2.7 (37%)
T _{max} (hr)	3 (1 - 6)	3 (1 - 6)	3 (1.5 - 6)
t _{1/2} (hr)	3.6 (33%)	3.0 (21%)	3.1 (19%)

Table 2. Pharmacokinetic parameters of cerivastatin metabolites M1 and M23 (geometric mean, CV) (study 159)

	1 x 0.2 mg	2 x 0.2 mg	1 x 0.4 mg
M ₁ AUC (µg*hr/L)	Indeterminate	1.69 (31%)	1.79 (42%)
M ₁ C _{max} (µg/L)	0.15 (35%)	0.23 (47%)	0.21 (47%)
M ₁ Ae (%)	1.7 (61%)	1.9 (51%)	1.8 (45%)
M ₂₃ AUC (µg*hr/L)	3.4 (35%)	6.0 (35%)	5.8 (29%)
M ₂₃ C _{max} (µg/L)	0.24 (40%)	0.56 (36%)	0.52 (29%)
M ₂₃ Ae (%)	6.8 (33%)	7.3 (36%)	7.0 (27%)

In the original submission, the sponsor established dose-proportionality over the range of 100 µg to 400 µg in terms of AUC and C_{max} in a randomized, parallel group, single, ascending dose study in healthy male volunteers (N=12 subjects/dose).

Table 3. Pharmacokinetic parameters (geometric mean) of a single dose ascending study

Parameter/Dose	100 µg	200 µg	300 µg	400 µg
AUC (µg*hr/L)	6.25	11.71	20.52	22.45
C _{max} (µg/L)	1.01	2.15	3.55	4.04
T _{max} (hr)	1.5 - 4.0	1.0 - 3.0	1.5 - 3.0	0.5 - 3.0
t _{1/2} (hr)	3.37	3.08	4.89	4.23

Conclusions:

1. The study 159 established the dose proportionality of the 0.2 mg and 0.4 mg doses.
2. The drug levels in current study seem to be lower than those in the original NDA.

Multiple Doses: Study D97-001 was a randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study in patients with primary hypercholesterolemia. Cerivastatin 800 µg (2 x 400 µg tablets) or placebo was administered once daily in the evening at mealtime for 28 days. The principal PK variables include AUC₀₋₂₄, C_{max}, t_{max} and t_½ on Day 28.

Table 4. Pharmacokinetic parameters of cerivastatin and metabolite following administration of 0.8 mg daily for 28 days (geometric mean, CV).

Parameter	Cerivastatin (n=27)	M ₁ (n=14)	M ₂₃ (n=14)
AUC (µg*hr/L)	67.0 (30%)	5.54 (48%)	17.0 (54%)
C _{max} (µg/L)	12.7 (41%)	0.55 (50%)	1.4 (47%)
T _{max} (hr)	1.4 (33%)	3.4 (53%)	4.5 (35%)
t _½ (hr) ¹	4.2 (20%)	3.6 (40%)	5.0 (39%)
24 hr Ae _{ur} (µg)	—	17.5 (37%)	51.8 (32%)
Ae _{ur} (%)	—	2.2%	6.5%

Note: AUC, C_{max}, t_{max} and t_½ are geometric means (CV), Ae_{ur} is arithmetic mean
1: n=13 for M₁

In a phase IIIb trial (study D96-001), a pharmacokinetic study was performed in two selected centers in sub-population (N=27). Full 24 hour plasma profiles were determined at visit 7 or 8 (on the 300 µg or 400 µg cerivastatin for 4 or 8 weeks) (Note: Raw data were not submitted. Therefore, the study results could not be validated.)

Table 5. Pharmacokinetic parameters of cerivastatin in hypercholesterolemic patients taking 0.3 mg or 0.4 mg (geometric mean, CV) (studies D96-008)

Parameter	Cerivastatin [geom.mean (CV)]	
	300 µg (n = 11)	400 µg (n = 16)
AUC ₀₋₂₄ (µg*hr/L)	27.7 (35%)	34.7 (27%)
C _{max} (µg/L)	5.1 (36%)	6.2 (24%)
T _{max} (hr)	1.8 (48%)	1.9 (36%)
t _½ (hr)	4.0 (34%)	3.9 (20%)

Table 6. Pharmacokinetic parameters of cerivastatin in hypercholesterolemic patients taking 0.3 mg, 0.4 mg or 0.8 mg (geometric mean, CV) (studies D96-008 and D97-001)

Parameter	Cerivastatin [geom.mean (CV)]		
	300 µg (n = 11)	400 µg (n = 16)	800 µg (n = 27)
AUC ₀₋₂₄ (µg*hr/L)	27.7 (35%)	34.7 (27%)	67.0 (30%)
C _{max} (µg/L)	5.1 (36%)	6.2 (24%)	12.7 (41%)
T _{max} (hr)	1.8 (48%)	1.9 (36%)	1.4 (33%)
t _½ (hr)	4.0 (34%)	3.9 (20%)	4.2 (20%)

Conclusions:

Dose proportionality may exist over the range of 300 µg and 800 µg. However, concrete conclusions could not be made since data sets were from two different studies and raw data of study D96-008 were not provided.

Bioequivalence:

The study 159 established the bioequivalence of 2x 0.2 mg tablets with a single 0.4 mg tablet. The 90% confidence intervals for AUC and C_{max} of the ratios of 1x400 µg: 2 x 200 µg were 0.92 – 1.01 and 0.82 – 1.00, respectively. Although statistical analyses have not been conducted for metabolites, M1 and M23, the results clearly show comparable AUC and C_{max} for M1 and M23.

Table 7. Pharmacokinetic parameters of cerivastatin following administration of different tablets and doses (geometric mean, CV)

	2 x 0.2 mg	1 x 0.4 mg
AUC (µg*hr/L)	18.1 (45%)	17.6 (44%)
C _{max} (µg/L)	3.0 (46%)	2.7 (37%)
T _{max} (hr)	3 (1 – 6)	3 (1.5 – 6)
t _{1/2} (hr)	3.0 (21%)	3.1 (19%)

Table 8. Pharmacokinetic parameters of cerivastatin metabolites M1 and M23 (geometric mean, CV) (study 159)

	2 x 0.2 mg	1 x 0.4 mg
M ₁ AUC (µg*hr/L)	1.69 (31%)	1.79 (42%)
M ₁ C _{max} (µg/L)	0.23 (47%)	0.21 (47%)
M ₁ Ae (%)	1.9 (51%)	1.8 (45%)
M ₂₃ AUC (µg*hr/L)	6.0 (35%)	5.8 (29%)
M ₂₃ C _{max} (µg/L)	0.56 (36%)	0.52 (29%)
M ₂₃ Ae (%)	7.3 (36%)	7.0 (27%)

Conclusions:

One 400 µg tablet is bioequivalent to two 200 µg tablets.

Pharmacodynamics:

Study D97-001 was a randomized, double-blind, placebo-controlled, parallel-group, multiple-dose study in patients with primary hypercholesterolemia. Cerivastatin 800 µg (2 x 400 µg tablets) or placebo was administered once daily in the evening at mealtime for 28 days. The pharmacodynamic (PD) variables including total cholesterol, direct LDL-C, calculated LDL-C, HDL-C, lipoprotein (a) and triglycerides were evaluated.

For LDL-C (direct), LDL-C (calculated) and total cholesterol, the mean percent decreases from baseline in the cerivastatin group were 41.0, 44.0 and 30.8%, respectively. In comparison, for LDL-C (direct), LDL-C (calculated) and total cholesterol, the mean percent change from baseline in placebo were 6.8, 1.2 and 2.1%, respectively. These

mean changes for cerivastatin 800 µg group were highly statistically different compared to the mean percent changes in the placebo group.

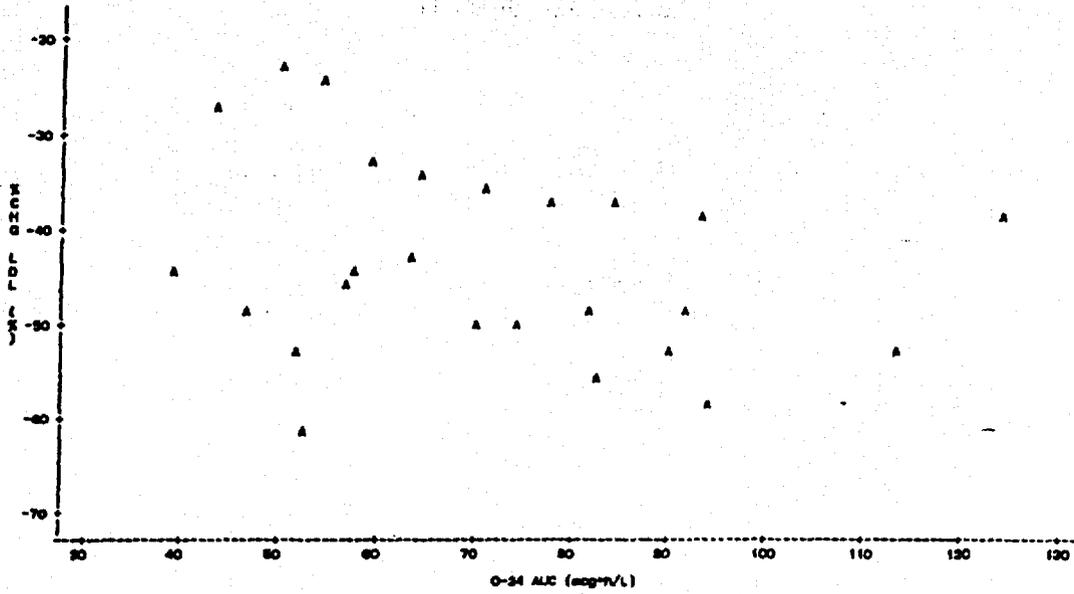
Pharmacokinetic/pharmacodynamic (PK/PD) analyses

The sponsor stated that a correlation analysis was performed in an attempt to correlate the percent change from baseline at Day 29 for LDL-cholesterol (calculated) with the pharmacokinetic parameters, AUC 0-24 and Cmax but no significant correlations were found

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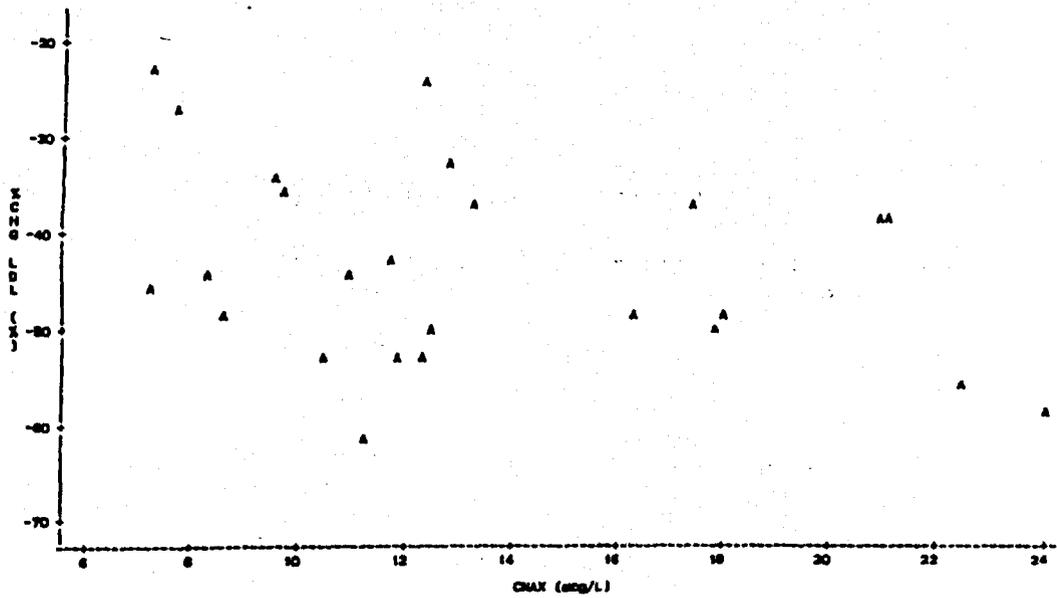
SUPPLEMENT TO TABLE 14.2/26.3
 PLOT OF PERCENT CHANGE FROM BASELINE AT DAY 28 FOR LDL-CHOLESTROL VERSUS 0-24 AUC
 CERIVASTATIN

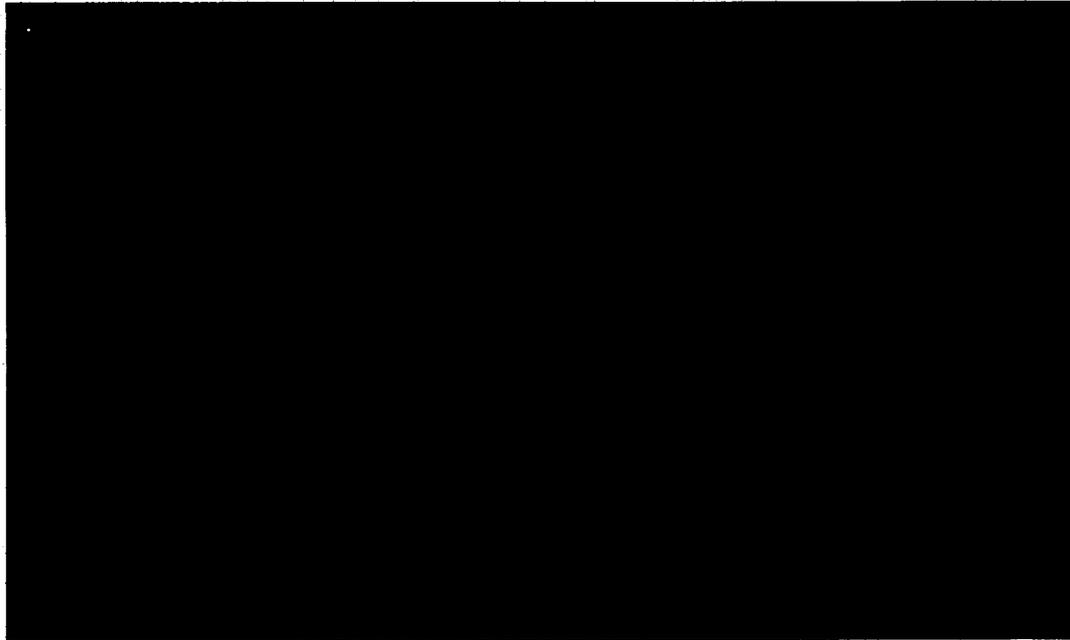
Plot of PCH33*AMC24. Legend: A = 1 obs, B = 2 obs, etc.



SUPPLEMENT TO TABLE 14.2/26.3
 PLOT OF PERCENT CHANGE FROM BASELINE AT DAY 28 FOR LDL-CHOLESTROL VERSUS CMAX
 CERIVASTATIN

Plot of PCH33*CMAX. Legend: A = 1 obs, B = 2 obs, etc.





Dissolution:



Labeling Comments:

The proposed labeling appears acceptable.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II finds that the supplement to NDA 20-740 is acceptable. However, it should be noted that the dissolution specification for the 0.4 mg is Q= [redacted] at [redacted] minutes, which is the same as those for the 0.1, 0.2 and 0.3 mg.

/S/ [redacted]

Hae-Young Ahn, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

J. Hunt

RD/FT initialed by J. Hunt, Deputy Director

/S/ [redacted]

5/3/99

CC: NDA 20-740, HFD-510 (Simoneau, Ysern, Parks, Orloff), HFD-870 (M. Chen, Ahn), HFD-850 (Lesko), HFD-340(Vish), CDR (Murphy)

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Clinical Pharmacology and Biopharmaceutics Review

NDA: 20-740

SUBMISSION DATE: September 20, 1996

BRAND NAME: BAYCOL®

GENERIC NAME: Cerivastatin Sodium (Bay w 6228) Tablets
50µg, 100µg, 200µg and 300µg

REVIEWER: Carolyn D. Jones, Ph.D.

SPONSOR: Bayer Corporation
West Haven, CT 06516

Type of Submission: Dissolution Data Review Report

SYNOPSIS:

BAYCOL® (cerivastatin sodium), a synthetic and pure enantiomer, is a new HMG-CoA reductase inhibitor that competitively inhibits the rate-limiting step of cholesterol synthesis, i.e., the conversion of hydroxymethylglutaryl-CoA to mevalonate. The drug is recommended for use in patients with hypercholesterolemia. The proposed dose range of cerivastatin is 200 µg to 300 µg given once daily in the evening, either with the evening meal or at bedtime. Bayer is proposing to market tablet strengths of 200 and 300 µg.

The sponsor is proposing the following dissolution specification which the Office of Clinical Pharmacology and Biopharmaceutics (OCPB)/Division of Pharmaceutical Evaluation II (DPEII) agreed to on an interim basis: USP Apparatus 2 (paddle) at [redacted] rpm
pH 6.8 citrate/phosphate buffer
Q= [redacted] % at [redacted] minutes.

[redacted]

However, it was understood that although on September 20, 1996 the sponsor had submitted to the agency cerivastatin dissolution data at three rotation speeds (50, 75 and 100 rpm) and at three different media ([redacted] and [redacted]) it was mislocated.

STUDY REPORT:

Initially, dissolution tests were conducted using a [REDACTED] using [REDACTED]. However, upon development of an [REDACTED] assay, the dissolution method was switched to the [REDACTED] method.

Production scale 0.05, 0.1 and 0.3 mg tablets and pilot scale 0.1 mg tablets were evaluated at three different media. The tests were performed using [REDACTED] Cerivastatin was [REDACTED]. Furthermore, no difference existed between the [REDACTED] and the [REDACTED]. All profiles showed complete dissolution at [REDACTED] minutes.

Using the same apparatus, the sponsor also investigated the effect of rotation speed using the 0.05 mg and 0.10 mg tablets at [REDACTED] using pH 6.8 citrate/phosphate buffer (See attached tables). Rotation speed had no effect on the dissolution of cerivastatin.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB)/Division of Pharmaceutical Evaluation II (DPEII) has reviewed the submission dated September 20, 1996 to NDA 20-740 and deems it acceptable. No further development of a dissolution method is required. The proposed specification USP Apparatus 2 (paddle) at [REDACTED] rpms
pH 6.8 citrate/phosphate buffer
Q= [REDACTED] at [REDACTED] minutes

which was originally accepted on an interim basis will be accepted as a final dissolution specification. Please convey this recommendation to the sponsor as appropriate.

COMMENTS NOT TO BE SENT TO THE SPONSOR:

1. The sponsor has [REDACTED] for the [REDACTED] mg tablets in the [REDACTED]. However, since data was submitted that bracketed this tablet strength (0.10 and 0.30 mg tablets), and no differences were observed, there is no reason to believe that the 0.20 mg tablet will behave differently.

[REDACTED]

6/3/97
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialed by Hae-Young Ahn, Ph.D., Team Leader [REDACTED] 6/4/97

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