CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-740/S008/S013

PHARMACOLOGY REVIEW(S)

NDA 20-740/S008 **Review Completed: June 19, 2000**

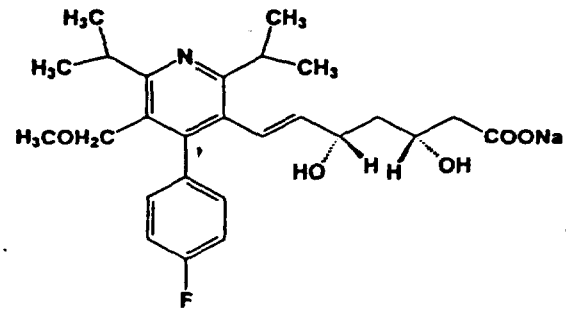
Sponsor: Bayer Corporation; 400 Morgan Lane; West Haven, CT 06516-4175

Date Submitted: September 22, 1999 **Date Received: September 23, 1999**

PHARMACOLOGY REVIEW OF INITIAL IND SUBMISSION
Supplement to NDA 20-740 #008 (September 22, 1999)

DRUG: Baycol (cerivastatin sodium tablets), 0.8 mg dose. BAY 6228

STRUCTURAL FORMULA:



CATEGORY: Lipid Lowering, "Statin"

INDICATION: Hypercholesterolemia

RELATED IND: NDA 20-740 is approved for currently marketed doses of 0.2 0.3 and 0.4 mg tablets. ~~This provides for increasing recommended dose to 0.8 mg~~

CLINICAL STATUS: Approved drug, efficacy supplement to market 0.8 mg tablet.

ANTICIPATED SPECIAL RISKS: Extensive listing is provided in the labeling.

BACKGROUND/SUPPLEMENT CONTENTS: As pointed out under supplement 002, the increased dose will change relative safety margins as reported in the label. The sponsor proposes to base estimations of relative exposure on Cmax,free rather than Cmax upon which comparisons were previously based. Under supplement 002, several intravenous studies were performed to characterize the toxicity of the metabolites found in humans, but not normally seen with oral dosing in animals. No new animal studies were presented in this submission. However, the issue of how to label the "safety margins" remained a question. Since the metabolites were active and different in humans and animals, it was determined under supplement 002 that in order to determine the safety margins based on Cmax or AUC of free drug that the expression had to express the total parent + metabolite of free drug. However, in this supplement (and subsequent responses to FDA inquiries on June 9 and 12, 2000 and a telecon with the sponsor on June 13, the sponsor clarified that the amount of metabolites is less than 10% of the total drug exposure and thus the calculation based on parent compound alone is adequate. I discussed this with the Biopharm team leader and she agreed. Thus, the

proposed labeling in the SNC submission of 6/9/00 is adequate to cover the multiples which are revised from the original application of Supplement 008 submitted September 22, 1999. The revision on June 2, 2000 occurred because more patient population PK data were obtained and used to calculate the safety margins. The original submission relied on a study in normal subjects and was not considered as relevant. This new determination in patients results in a more conservative estimate than the original since the patient levels were higher than those detected in the initial study in normal subjects. The multiples were adjusted appropriately and the labeling provided in the submission of June 9, 2000 is acceptable for the pharmacology sections.

RECOMMENDATION

Pharmacology recommends approval of NDA 20-740 supplement 008 pending the appropriate modification of the label to reflect animal and human exposure comparisons based on Cmax and/or AUC of free parent compound as provided in the submission of June 9, 2000.

TO BE COMMUNCIATED TO THE SPONSOR

The labeling for the preclinical sections proposed in the June 9, 2000 submission (Revised Package Insert as of June 2, 2000) is acceptable. Since the carcinogenicity studies were performed with dietary administration, this should be made clear in the carcinogenicity sections. The following terminology is recommended:

"Carcinogenesis, Mutagenesis, Impairment of Fertility: A 2-year study was conducted in rats **with dietary administration resulting in** average daily doses..."

In a 2-year carcinogenicity study **conducted** in mice **with dietary administration resulting in** average daily doses..

/S/

Ronald W. Steigerwalt, Ph.D.
Supervisory Pharmacologist, DMEDP

6/20/00

cc: IND Arch
HFD510
HFD510/Steigerwalt/Koch
Review Code: AP
Filename:

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APPENDIX

(labeling and pertinent data to support proposed "margins of exposure" taken from June 2, 2000 version of label

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WITHHOLD 2 pages

Draft

Labeling

Attachment 2

Pharmacokinetic and efficacy parameters of cerivastatin and relevant metabolites

Plasma Exposure at steady state after dosing with 0.8 mg daily						
	cerivastatin	M1	M23	cerivastatin	M1	M23
	Cmax (mcg/l)			AUC0-24 (mcg*h/l)		
Human	12.7	0.55	1.4	67	5.54	17

Reference: Bayer Study No. D97-001

Free Fraction fu [%] in plasma		
	cerivastatin	M23
Human	0.7	3.34
Dog	1.85	13.6
Rat	2.5	25.9
Mouse	1.3	nd
Rabbit	2.0	nd

nd = not detected or not measured

Reference (cerivastatin): Bayer Report PH-20067 (rat, dog, man), PH-24850 (mouse), data submitted May 2000 (rabbit)

Reference (M23): Bayer Report PH-29129

Metabolite Profile maximum detected after single oral doses of cerivastatin								
	cerivastatin	M1	M8	M21	M23	M27	M28	M30
	[% in plasma extract]							
Human	71	6.7	nd	nd	11.5	nd	nd	nd
Dog	88	5.8	11.2	nd	nd	nd	nd	nd
Rat	66	4.9	nd	2.5	nd	nd	nd	4.0
Mouse	nd	nd	nd	7.2	nd	55	41	nd
	[% in liver extract]							
Dog	nd	nd	nd	nd	nd	nd	nd	nd
Rat	83	5.6	nd	51	nd	nd	nd	7.8
Mouse	nd	nd	nd	6.2	nd	19	30	1.0

nd = not detected

Reference (animal data): Drug Metab Dispos 1998, 26:640-652

Reference (human data): Bayer Report PH-25040

HMG-CoA reductase inhibition rat liver preparations [IC50 * 10-9]			
	cerivastatin	M1	M23
in vitro	1.1	1.7	1.0

Reference: Arteriosclerosis 1997, 130(suppl.): S25