Tablets MEVACOR®
(Lovastatin)

Environmental Assessment - Categorical Exclusion

1. **Date**

March 20, 1997

2. **Name of Applicant**

Merck Research Laboratories
Merck and Co., Inc.

3. **Address**

Sumneytown Pike
West Point, PA 19486

4. **Description of Proposed Action**

4.a. **Requested Action - Categorical Exclusion**

Merck & Co., Inc. is filing a Supplemental New Drug Application (SNDA) requesting the approval of revisions to the product circular for MEVACOR® Tablets (lovastatin). The SNDA supports a new primary prevention indication based on the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) and a revised recommendation to monitor liver function tests.

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.31(b). The production of MEVACOR® Tablets meets the requirements of a categorical exclusion under 21 CFR §25.31(b) because the estimated concentration of drug substance lovastatin at the point of entry, referred to as the Expected Introduction Concentration (EIC), into the aquatic environment will be [redacted] To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

Charles L. Hyman, M.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2850
215 652 5000

October 27, 1998

DESK COPY

MERCK
Research Laboratories

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Fax No.: 301.443.9282

Dear Dr. Sobel:

NDA 19-643/S-055: **MEVACOR™** (Lovastatin)
Response to Request for Information

Reference is made to the Supplemental New Drug Application 19-643/S-055 for MEVACOR™ (Lovastatin) submitted on April 28, 1998. Reference is also made to telephone conversations on October 15 and 16, 1998 between Dr. Charles Hyman, Merck Research Laboratories (MRL) and Dr. Mary Parks, FDA, during which Dr. Parks requested additional information on the lipid parameters of the NHANES reference group. By this letter, MRL is providing the requested information in the attached table.

Questions concerning this information should be directed to Charles L. Hyman, M.D. (610/397-2850) or, in my absence, Bonnie J. Goldmann, M.D., Ph.D. (610/397-2383).

Sincerely,

Charles L. Hyman, M.D.
Director, Regulatory Affairs

Attachment

Federal Express #1

Desk Copies: Federal Express #1 Dr. David Orloff, HFD-510, Rm. 14B04
Federal Express #1 Dr. Mary Parks, HFD-510, Rm. 14B04
Federal Express #1 Ms. Margaret Simoneau, HFD-510, Rm. 14B04

q\hark\mev\fda\026L.doc

U.S. Reference Population Based Upon U.S. NHANES III*

Laboratory Parameter	U.S NHANES III		
	Men	Women	Combined
LDL-C (mg/dL)**			
N	587	346	933
(Estimated Population)	(22,511,316)	(15,280,569)	(37,791,885)
Min	30.0	40.0	30.0
Mean	139.2	146.8	142.2
Median	138.0	145.0	141.0
Max	282.0	361.0	361.0
SD	34.9	40.1	37.3
Total-C (mg/dL)			
N	651	380	1031
(Estimated Population)	(24,885,413)	(16,981,628)	(41,867,041)
Min	103.0	104.0	103.0
Mean	217.7	236.7	225.4
Median	213.0	229.0	218.0
Max	446.0	464.0	464.0
SD	41.8	47.1	45.0
HDL-C (mg/dL)			
N	644	378	1022
(Estimated Population)	(24,512,937)	(16,836,100)	(41,349,037)
Min	20.0	14.0	14.0
Mean	46.5	56.1	50.4
Median	44.0	54.0	47.5
Max	121.0	109.0	121.0
SD	14.5	16.9	16.2
LDL-C/HDL-C			
N	587	346	933
(Estimated Population)	(22,511,316)	(15,280,569)	(37,791,885)
Min	0.4	0.5	0.4
Mean	3.2	2.9	3.1
Median	3.1	2.7	3.0
Max	7.1	17.3	17.3
SD	1.2	1.9	1.5
Total-C/HDL-C			
N	644	378	1022
(Estimated Population)	(24,512,937)	(16,836,100)	(41,349,037)
Min	1.6	1.7	1.6
Mean	5.1	4.7	4.9
Median	4.9	4.3	4.6
Max	15.5	22.1	22.1
SD	1.7	2.6	2.1
TG (mg/dL)***			
N	599	355	954
(Estimated Population)	(23,183,069)	(16,010,862)	(39,193,930)
Min	32.0	38.0	32.0
Mean	174.8	166.9	171.6
Median	128.0	132.0	130.0
Max	3616.0	800.0	3616.0
SD	253.5	113.5	208.0

* Analysis weight used (WTPFHSD1), for special analyses where fasting time may be an important factor, was computed for mobile examination center (MEC) and home examined persons who were scheduled and examined in the morning session.

** Calculated for examinees who were instructed to fast and did fast at least nine hours and whose serum triglyceride values did not exceed 400 mg/dL.

*** Estimated for examinees who were instructed to fast and did fast at least nine hours.

Charles L. Hyman, M.D.
Director
Regulatory Affairs

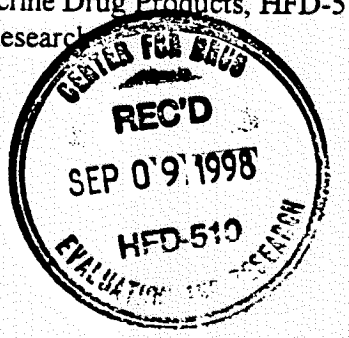
Merck & Co., Inc.
P.O. Box 4
West Point PA 19486
Fax 610 397 2516
Tel 610 397 2850
215 652 5000

September 3, 1998

DESK COPY

MERCK
Research Laboratories

Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Fax No.: 301.443.9282

Dear Dr. Sobel:

Dear Dr. Sobel:

NDA 19-643/S-055 (AFCAPS/TexCAPS)
MEVACOR® (lovastatin)
RESPONSE TO REQUEST FOR INFORMATION

Reference is made to the above supplemental New Drug Application (NDA). Reference is also made to telephone conversations between Dr. Charles Hyman of MRL and Dr. Mary Parks, FDA on August 19, 1998, and September 2, 1998, during which additional information was requested regarding the impact of baseline TC/HDL-C on treatment in the AFCAPS study. Specifically, Dr. Parks requested data on rates of the first primary endpoint according to treatment group versus baseline TC/HDL-C ratio of $\leq$, or > 5. This letter provides these data.

Table 1 shows sample sizes, cases, person-years at risk, rates, and relative risk with 95% confidence intervals for the total cohort and the requested subgroups. As would be expected, the event rate was higher for patients with baseline TC/HDL-C > 5.0 compared to those with lower baseline ratios. However, and of interest, there was a substantive reduction in risk of a primary endpoint in those with a baseline TC/HDL-C $\leq$ 5.0 (65% reduction - note that the wide confidence interval reflects imprecision due to the small number of persons and events) as well as those with TC/HDL-C > 5.0. While the estimates of relative risk appear numerically different, there was considerable overlap in the confidence intervals and the estimates were not different statistically as there was no significant interaction (p=0.290) between treatment and baseline TC/HDL-C when evaluated as a continuous variable in a model with other significantly associated covariables. The latter method of assessment was prespecified in the Data Analysis Plan.

Table 1.
AFCAPS/TexCAPS - Primary Endpoint
Cases, Person-Years at Risk, Crude Rates, and Relative Risks

Subgroup	Treatment Group	N	Cases	PYR[1]	Rates[2]	Relative Risk (95% CI)[3]
Total Cohort	Lovastatin	3304	116	17041	6.81	0.63 (0.50, 0.79)
	Placebo	3301	183	16865	10.85	
Baseline TC/HDL-C ≤ 5.0	Lovastatin	383	6	2024	2.97	0.35 (0.14, 0.89)
	Placebo	406	18	2126	8.46	
Baseline TC/HDL-C > 5.0	Lovastatin	2921	110	15018	7.32	0.65 (0.51, 0.83)
	Placebo	2895	165	14739	11.19	

[1] PYR= Person years at risk
[2] Endpoints per 1000 PYR
[3] Cox proportional hazard model, stratified by study center and gender.

Table 2 shows a breakdown of the risk factors for CHD in the two treatment groups and separately for TC/HDL-C ≤, > 5.0 at baseline. In addition, male gender, while no longer an individual NCEP risk factor is included. Please note, as per the study protocol all participants met the age criteria for risk. As expected, there are a greater number of persons with HDL-C < 35 mg/dl in the subgroup with the high ratio. The treatment groups appear generally well balanced for the listed risk factors.

Table 2.
Number (%) of Participants with CHD Risk Factors
by Category of Baseline TC/HDL-C Ratio

Baseline TC/HDL-C	Positive Risk Factor	Lovastatin N (%)	Placebo N (%)
≤ 5.0	Smoking	43 (11.2)	34 (8.4)
	Hypertension	70 (18.3)	78 (19.2)
	Family History	54 (14.1)	57 (14.0)
	Diabetes	6 (1.6)	8 (2.0)
	Baseline HDL-C < 35 mg/dL	1 (0.3)	1 (0.2)
	Male[‡]	311 (81.2)	323 (79.6)
>5.0	Smoking	386 (13.2)	355 (12.3)
	Hypertension	649 (22.2)	651 (22.5)
	Family History	443 (15.2)	481 (16.6)
	Diabetes	78 (2.7)	63 (2.2)
	Baseline HDL-C < 35 mg/dL	1149 (39.3)	1145 (39.6)
	Male[‡]	2494 (85.4)	2480 (85.7)

[‡] Note: male sex is no longer a NCEP risk factor but is reported for information purposes; all participants meet the age criteria for CHD risk.

I hope these data are helpful and address your questions. If you have further questions, or need additional information please contact Charles L. Hyman, M.D. (610. 397.2850) or, in my absence, Bonnie J. Goldmann, M.D. (610.397.2383).

Sincerely,

Charles L. Hyman, M.D.
Director, Regulatory Affairs

Federal Express #1

Desk Copies: Federal Express #1 Dr. David Orloff, HFD-510, Rm. 14B04
Federal Express #1 Dr. Mary Parks, HFD-510, Rm. 14B04
Federal Express #1 Ms. Margaret Simoneau, HFD-510, Rm. 14B04