Memo; Statistical Review AFCAPS/TEXCAPS

Date: December 9, 2004
Between: Mary Parks, M.D., Clinical Team Leader (HFD-510)
and
Joy D. Mele, M.S., Statistical Reviewer (HFD-715)
Subject: Mevacor OTC NDA 21213

This memorandum addresses Section 1.6.1.2.5 entitled "Defining the Benefit of Lovastatin 20 mg once daily in the Mevacor OTC Eligible Population".

The applicant (Merck Research Laboratories) performed analyses of the AFCAPS/TEXCAPS data to estimate the possible effect of 20 mg (the proposed OTC dose) of lovastatin on clinical endpoints in an OTC eligible population. The selection criteria for AFCAPS/TEXCAPS and the OTC-eligible population are summarized in Table 1.

Table 1. Selection criteria for Study AFCAPS/TEXCAPS and the proposed OTC-eligible population

	AFCAPS/TEXCAPS	OTC-eligible
Age	Male≥45; Female≥55	Male≥45; Female≥55
LDL-C	125-129 if TC/HDL>6 130-190	130-170
Risk factors HDL smoker family history high BP	Must have low HDL Male ≤45; Female≤55 yes yes controlled BP only	At least one risk factor <40 yes yes yes
Evidence of CVD	Excluded	Excluded

The primary difference between the criteria is that AFCAPS/TEXCAPS patients all had "low" HDL while the OTC patients must have at least one risk factor which may or may not include low HDL.

Reviewer's Comments:
The results of AFCAPS/TEXCAPS may not be applicable to patients who do not have low HDL; however, evidence from the Heart Protection Study suggests that similar patients without evidence of cardiovascular disease who have high HDL and a risk factor for CHD (such as diabetes, hypertension or peripheral/cerebral vascular disease) receive beneficial effects from statin therapy.

The applicant looked at three subgroups of patients from AFCAPS/TEXCAPS; 1) patients meeting the OTC eligible criteria at baseline, 2) patients who reached goal without titrating up to 40 mg and 3) patients who achieved an LDL of less than 130 on treatment (these groups are described in more detail in Dr. Parks' review).

Reviewer's Comments:
Patients in Groups 2 and 3 were selected based on their response and so those groups do not represent proper subgroups (i.e. randomized groups); therefore, the results of Groups 2 and 3 are not reviewed here. The drawback to Group 1 is that about ½ the patients were titrated to the 40 mg dose. In fact the applicant stated that because of the titration, "direct estimation of the benefit of 20 mg … is not possible" (page D-61 of the NDA).

The results for the OTC eligible subgroup and the complete AFCAPS/TEXCAPS population from the NDA under review (2004) and from a previous submission dated December 10, 1999 are summarized in the table below. Note that the definition of OTC eligible differed between the submissions; in the previous submission, men had to be 40 or older, patients with a history of high blood pressure were excluded and there was no criteria for HDL.

Table 2. AFCAPS/TEXCAPS Event rates and Number-Needed-to-Treat (NNT) as reported by the applicant in NDA's submitted in 1999 and 2004

	Placebo	Lovastatin	NNT
1999 NDA			
All Pts			
Events	183/3301	116/3304	
5 YR K-M rate	5.2%	3.3%	54
OTC- Eligible			
Events	108/1921	60/1884	
5 YR K-M rate	5.3%	3.0%	43
2004 NDA			
All Pts			
Events	184/3301	116/3304	
6 YR K-M rate	6.8%	3.8%	34
OTC- Eligible			
Events	88/1449	48/1433	
6 YR K-M rate	7.5%	3.5%	25
FDA review of AFCAPS/TEXCAPS All Pts.			
Events	183/3301	116/3304	
End of Study K-M Rate	7.2%	5.1%	48

Event=cardiac death, fatal or non-fatal MI or unstable angina

<u>Reviewer's Comments:</u>
The difference between the rates and the NNT in the above table is due to the length of observation periods; the 1999 rates were based on 5 year estimates while 2004 rates are based on 6-year estimates. The last row shows the Kaplan-Meier estimates presented in the FDA review of AFCAPS/TEXCAPS which is much closer to the 5-year treatment effect. It is worth noting that there were only two centers in AFCAPS/TEXCAPS and one center (with 43% of the patients) had a maximum follow-up of 5.1 years. A small number of patients completed 6 years of treatment. This reviewer concludes that the NNT estimates presented in the submission under review (the 2004 submission) are not acceptable and underestimate the NNT.

Overall this reviewer thinks that there is a body of evidence from several statin trials that suggest that a wide range of patients may receive clinical benefit from statin therapy; however, none of the clinical endpoint trials were conducted in a population limited to Merck's targeted OTC population and treated with only 20 mg of Mevacor. Also as mentioned by FDA reviewer David Hoberman in a statistical review of the 1999 NDA, a critical factor to consider is that "the compliance in AFCAPS/TEXCAPS is probably much greater than that in a true OTC setting." Estimates from a closely monitored population may not represent what we could expect in an OTC population.