Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee December 13, 2007

Topic: The committee evaluated data submitted by Merck & Co., Inc. to support the over-the-counter use of Mevacor (lovastatin) 20 milligrams a day to help lower cholesterol which may prevent a first heart attack.

These summary minutes for the December 13, 2007 joint meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee were approved on December 31, 2007.

I certify that I attended the December 13, 2007 joint meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

_____/s/_____
Diem-Kieu H. Ngo, Pharm.D.

_____/s/_____
Mary E. Tinetti, M.D.
(Chair)

Summary Minutes of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee
December 13, 2007

The following is the final report of the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee held on December 13, 2007. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder07.htm

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information office.

The Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration met on December 13, 2007 at the Hilton Washington DC/Silver Spring, 8727 Colesville Road, Silver Spring, Maryland. Mary Tinetti M.D., chaired the meeting. There were approximately 280 in attendance.

Attendance:

Nonprescription Drugs Advisory Committee Members present (voting):
Mary E. Tinetti, M.D.; Ruth M. Parker, M.D.; Robert E. Taylor, M.D., Ph.D., F.A.C.P.; William H. Shrank, M.D., M.S.H.S.

Nonprescription Drugs Advisory Committee Members absent:
Ernest B. Clyburn, M.D.; Garret A. FitzGerald, M.D.; Ralph B. D'Agostino, Ph.D.; Marie R. Griffin, M.D.; Jan L. Hewett, J.D., B.S.N.

Endocrinologic and Metabolic Drugs Advisory Committee Members present (voting):
Kenneth D. Burman, M.D.; Clifford J. Rosen, M.D.; Sonia Caprio, M.D.; Michael A. Proschan, Ph.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members absent:
Nelson B. Watts, M.D. (Chair); Thomas P. Bersot, M.D., Ph.D.; Jessica W. Henderson, Ph.D.; Katherine M. Flegal, Ph.D.; Allison B. Goldfine, M.D.

Temporary Voting Members:
Arthur Flatau, Ph.D. (Patient Representative); Stephen P. Glasser, M.D.; Arthur A. Levin, M.P.H. (Consumer Representative); Richard A. Neill, M.D.; Thomas G. Pickering, M.D., D.Phil.

Industry Representative (non-voting):
Edward B. Nelson, M.D., Ph.D. (NDAC)

FDA Participants (non-voting):
Charles Ganley, M.D.; Andrea Leonard-Segal, M.D.; Curtis Rosebraugh, M.D., M.P.H.; Eric Colman, M.D.

Open Public Hearing Speakers:
Sandra Lewis, M.D., F.A.C.C.; Suzanne Hughes, M.S.N., R.N.; Stewart Levy, R.Ph.; David Nash, M.D., M.B.A.; Wm. James Howard, M.D.; Penny Kris-Etherton, Ph.D., R.D.; Cynthia Reilly, R.Ph.; David Randall; Ria Eapen; Marci Bough, Pharm.D.; Jesse M. Polansky, M.D., M.P.H.; Susan K. Nelson; Sidney Wolfe, M.D.

On December 13, 2007, the committees met in joint session to evaluate data submitted by Merck & Co., Inc. to support the over-the-counter use of Mevacor (lovastatin) 20 milligrams a day to help lower cholesterol which may prevent a first heart attack.

On December 13, 2007, Mary Tinetti, M.D., (NDAC Chair) called the meeting to order at 8:00 a.m. The Committee members and the FDA participants introduced themselves. The conflict of interest statement was read into the record by Diem-Kieu H. Ngo, Pharm.D., Designated Federal Official (DFO). The agenda for the meeting was as follows:

8:00 a.m.	Call to Order and Opening Remarks	**Mary E. Tinetti, M.D.** Chair, Nonprescription Drugs Advisory Committee
	Introduction of Committee	
	Conflict of Interest Statement	**Diem-Kieu H. Ngo, Pharm.D.** Designated Federal Official
8:10 a.m.	FDA Introductory Remarks	**Andrea Leonard-Segal, M.D.** Director, Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products, CDER, FDA
APPLICANT PRESENTATION		
8:30 a.m.	Introduction	**Edwin Hemwall, Ph.D.** Executive Director Worldwide OTC Regulatory & Scientific Affairs Merck Research Laboratories
8:35 a.m.	Public Health Opportunity	**Valentine Burroughs, M.D., M.B.A.** Associate Professor of Medicine Mount Sinai Medical School, NYC
8:45 a.m.	Lovastatin: Safety and Efficacy	**Ingrid Adamsons, M.D., M.P.H.** Senior Director, Clinical Research Merck Research Laboratories
9:00 a.m.	CUSTOM Study Overview	**Jerry Hansen, R.Ph., M.B.A.** Executive Director, Consumer Behavior Research Rx-to-OTC Switch Merck Research Laboratories
9:10 a.m.	SELECT Study Results	**Edwin Hemwall, Ph.D.** Executive Director Worldwide OTC Regulatory & Scientific Affairs Merck Research Laboratories
9:35 a.m.	Education, Support, and Monitoring	**Saul Shiffman, Ph.D.** Professor of Psychology, Psychiatry & Pharmaceutical Sciences, University of Pittsburgh

9:45 a.m.	Marketing Plans	**George Quesnelle** President Consumer Healthcare – North America GlaxoSmithKline Consumer Healthcare
9:55 a.m.	Conclusion	**Edwin Hemwall, Ph.D.** Executive Director Worldwide OTC Regulatory & Scientific Affairs Merck Research Laboratories
10:00 a.m.	**BREAK**	

FDA PRESENTATION

10:15 a.m.	LDL-C vs. TC Labeling Paradigm	**Eileen, Craig, M.D.** Medical Officer Division of Metabolism and Endocrinology Products
10:30 a.m.	History of the Label and Label Comprehension Studies	**CAPT Laura E. Shay, R.N., M.S., C-ANP** Social Science Analyst Division of Nonprescription Clinical Evaluation
10:50 a.m.	Self-Selection Study	**Linda Hu, M.D.** Medical Officer Division of Nonprescription Clinical Evaluation
11:25 a.m.	Hepatic Safety Study	**Shewit Bezabeh, M.D., M.P.H.** Medical Epidemiologist Division of Drug Risk Evaluation
11:45 a.m.	Statins and a Data Mining Signal for ALS	**Eric Colman, M.D.** Deputy Director, Lipid Team Leader Division of Metabolism and Endocrinology Products
12:10 p.m.	Questions/Clarifications	
12:30 p.m.	**LUNCH**	
1:30 p.m.	Open Public Hearing	
2:30 p.m.	Questions/Discussion	
3:15 p.m.	**BREAK**	
3:30 p.m.	Questions/Discussion	
5:00 p.m.	**ADJOURNMENT**	

Questions to the Committee:

1. The NCEP ATP-III guidelines use LDL-C as the basis for determining therapeutic targets and selecting populations for drug treatment and ongoing management. The FDA advisory committee that convened in January 2005 to discuss nonprescription lovastatin 20 mg agreed that the population of subjects selected using an LDL-based label paradigm was appropriate for drug treatment.

Do you believe that a total cholesterol-based label paradigm is an appropriate approach to selecting patients for use of nonprescription lovastatin and ongoing management? Please state the reasons for your position.

Committee Discussion:
(See Transcript for Complete Discussion)

The committee proposed to change the wording of the question to:
Is the broader target population that will be appropriate for a cholesterol versus a LDL paradigm acceptable?

Yes: 2 No: 10 Abstain: 1

2. At previous joint Nonprescription Drug Advisory Committee (NDAC) and Endocrine and Metabolic Drugs Advisory Committee meetings, the difficulty in developing a label which adequately conveys to consumers all the information necessary to make a correct self-selection has been discussed. The NDAC members, in September, 2006, at an advisory committee meeting devoted to consumer study design issues stated that it was reasonable to use hierarchies based on safety and efficacy consideration, to assess appropriate self-selection for products that have multiple self-selection criteria. Since that meeting we have been advising sponsors to use the hierarchy approach. You have seen examples of different hierarchies used to assess self-selection of nonprescription lovastatin 20-mg.

Was there a hierarchy presented today that should be used for the basis of a regulatory decision? Please state which one and provide your reasoning. Is there another hierarchy that you would suggest for this purpose? If so, please state the elements that should be part of that hierarchy.

Committee Discussion:
The committee did not take a vote on this question since the committee did not have enough information on hierarchies, but a discussion transpired instead. The committee noted that hierarchy data is useful as a concept but not helpful in helping this product towards approval status. The committee recommended that if the Agency wants to use hierarchies, it should start with safety, then add in benefits. Both aspects are relevant. In the case of OTC statins, the committee felt that the individual components (e.g. pregnancy, age, LDL level, CV risk factors, etc.) are all evidence-based and, as such, there is no basis to eliminate any of them in considering appropriate self-selection.
(See Transcript for Complete Discussion)

3. Do the results from the SELECT self-selection study demonstrate that OTC consumers could make an appropriate self-selection decision? In your deliberation please consider how these groups should be factored into our thinking about appropriate self-selection.

a. Those who receive little benefit because they are at lower risk for CHD
b. Those who receive sub-optimal benefit because they are at higher risk for CHD than the population identified on the label

c. Those who might switch from a prescription statin such as atorvastatin, simvastatin, or rosuvastatin to lovastatin 20 mg, a less potent alternative.
d. Those who might take their prescription statin or other prescription lipid-altering drug in addition to the OTC statin

Committee Discussion:
The committee noted concerns over high risk patients who are already on appropriate therapy and may switch to suboptimal therapy. The committee also noted concerns about drug interactions, the use of OTC statins with prescription statins and other lipid lowering drugs, and more side effects with more medication. The committee was also concerned with the use of OTC statins by those at low (<5%) risk. The available data on adverse effects remains insufficient to determine whether benefits outweigh harms in this low risk group. Careful studies of adverse effects (muscle weakness, neuropathy, depression, etc) are needed in the spectrum of individuals who reflect those who would take this medication in the OTC setting. A concern was raised about whether parents may purchase OTC products for their children. There were also concerns raised regarding the FDA's lack of authority to regulate OTC marketing and advertising. A comment was made regarding the proposal to sell Mevacor Daily™ in stores with pharmacies only but not all pharmacies are open 24 hours even though the stores are open 24 hours. (See Transcript for Complete Discussion)

Yes: 2 **No: 11** **Abstain: 0**

4. To address the safety of lovastatin in the nonprescription setting:

a. Do the data support adequate consumer understanding of the warning concerning pregnancy and appropriate self-selection by women of childbearing potential? If not, what further data would be needed?

Committee Discussion:
(See Transcript for Complete Discussion)

Yes: 9 **No: 4** **Abstain: 0**

b. Do the data support adequate consumer understanding of the muscle pain warning? If not, what further data would be needed? When answering, please consider the self-selection responses of those who were already on statins and chose to switch to the OTC product or to take both products.

Committee Discussion:
Mention was made to ensure that the labeling and consumer comprehension include muscle weakness as well as muscle pain. (See Transcript for Complete Discussion)

Yes: 12 **No: 1** **Abstain: 0**

c. Do the data demonstrate that consumers with common asymptomatic liver disease can safely use lovastatin 20 mg without liver function monitoring? If not, could labeling minimize this risk?

Committee Discussion:
(See Transcript for Complete Discussion)

Yes: 9 **No: 3** **Abstain: 1**

d. FDA and others have observed a data mining signal for amyotrophic lateral sclerosis (ALS) with statins. Retrospective analyses of data from large, long-term trials of primary and secondary CAD prevention revealed similar incidence rates of ALS in statin and placebo-treated patients. There is an ongoing case-control study examining the question of whether statins increase the risk for ALS. This study is expected to be completed in mid-to-late 2008. Considering the self-selection data and risk versus benefit of taking a statin for coronary heart disease prevention, how does the ALS data mining signal impact on OTC availability of statins?

Committee Discussion:
The committee noted that there is insufficient data to warrant action and that there is no compelling data to hold up OTC status at this time. Action may be taken if further data warrants it in the future. It was also noted that the FDA may consider looking at a signal for hemorrhagic stroke. The latter is a potential issue because low LDL as well as stain use have been associated, albeit inconsistently, with an increased risk of hemorrhagic stroke in both RCT and observational studies. (See Transcript for Complete Discussion)

5. Subjects in the CUSTOM actual use study used a different label than subjects in the SELECT label comprehension studies and SELECT self-selection study. In the absence of actual use data from the SELECT label, can we bridge the actual use data from the CUSTOM actual use study to the following consumer behaviors:

- follow-up cholesterol testing
- consumer action if the LDL target is not met
- consumer action if a side effect such as muscle pain develops

If not, what additional data are needed? Address this question for the LDL–C Label and, if your answer to question 1 is yes, address this question for the Total-C label.

Committee Discussion:
The committee did not discuss this question due to time limitations.

6. Should FDA approve nonprescription lovastatin based on the data presented at this meeting? Why or why not? What additional data is needed, if any?

Committee Discussion:
It was clarified that the term "nonprescription" means over-the-counter (OTC). Those voting in favor noted the public health issue of hypercholesterolemia and the large number of untreated individuals. The committee expressed the following concerns: consumers could not determine if the Mevacor Daily™ product was appropriate for them or not (self-selection problem) as reflected by the large percentage of people who inappropriately self selected OTC statins; role of the physician is unclear – majority of consumers noted they would discuss with MD; need to see Actual Use studies with the actual proposed label and not another label; unclear if consumers can self-diagnose the condition; over-treatment of low risk patients and under-treatment of high risk patients; the benefits and risks have not been tested in large scale studies in the real world OTC environment; no evidence to date to show that there will be appropriate monitoring and follow-up in an OTC setting which is important as this drug needs to be taken for life and health status and other medications are likely to change over time. Data presented to date do not convey that consumers can make an informed decision. The lack to FDA input into advertising was raised as an issue as well. (See Transcript for Complete Discussion)

Yes: 2 No: 10 Abstain: 1

The meeting was adjourned at approximately 5:00 p.m. on December 13, 2007.