

**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: September 26, 2005

FROM: Thomas P. Laughren, M.D.
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HFD-130

SUBJECT: October 25 & 26, 2005 Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC)

TO: Members, PDAC

Wednesday, Oct 26th: Emsam (selegiline patch)—Question of whether or not dietary restrictions should be required for the 20 mg dose of Emsam

The second day of the PDAC meeting will focus on NDAs 21-336 and 21-708 for Emsam (selegiline transdermal system--STS) for major depressive disorder (MDD). The two NDA numbers refer to applications to support short-term and longer-term safety and efficacy, respectively. Emsam is a patch formulation for selegiline, an irreversible inhibitor of monoamine oxidase (MAO). The original NDA for STS was submitted 5-24-01, and a nonapproval letter was issued 3-25-02. The basis for this nonapproval action was a lack of sufficient efficacy data to support the approval. The sponsor subsequently conducted an additional short-term efficacy trial and resubmitted the application on 7-31-03, including the results of the additional short-term efficacy trial and also results from a longer-term efficacy trial. We reviewed this resubmission and issued an approvable letter on 1-30-04. The sponsor responded to this second action letter on 5-26-05.

Although the efficacy issues for these NDAs have been resolved, as have most other issues, there remain several issues that are still under review. Among these remaining issues is a question about whether or not dietary restrictions are needed for the 20 mg Emsam patch. It is well-known that orally administered MAOIs have a risk of what is known as the “cheese reaction.” The dietary amine tyramine is a pressor substance that is ordinarily metabolized by MAO-A in the gut wall, thus preventing its entry into the systemic circulation where it would elevate blood pressure. Orally administered nonselective MAOIs (e.g., phenelzine) block MAO-A in the gut wall, thus allowing entry of tyramine into the systemic circulation. Certain foods, e.g. aged cheeses, contain relatively higher concentrations of tyramine, resulting in higher systemic exposure to tyramine, hence the name “cheese reaction”. The patch formulation of selegiline

would be expected to have an advantage over orally administered MAOIs because it bypasses the gut wall, thus theoretically avoiding a substantial inhibition of gut wall MAO-A. The sponsor has accumulated a substantial amount of data that they feel support the view that at least the 20 mg Emsam patch is relatively free of the risk for a “cheese reaction,” but they are willing to accept dietary restrictions for the two higher patch strengths (30 and 40 mg), because there are relatively little data supporting the safety of these doses with regard to a potential for the cheese reaction. Thus, they have argued that the 20 mg patch should not have dietary restrictions. A lack of dietary restrictions for the 20 mg patch would be a substantial benefit for patients and prescribers, because having to worry about diet is a major disincentive to using the orally available MAOIs in the US. On the other hand, the clinical reviewer for these NDAs, Greg Dubitsky, M.D., has reviewed the data accumulated by the sponsor and disagrees that the Emsam 20 mg strength can be safety marketed without dietary restrictions. The Division of Psychiatry Products has not yet reached a conclusion on this matter, and seeks the advice of the PDAC before reaching a conclusion.

The background package included Dr. Dubitsky’s review of the sponsor’s 5-26-05 response to the agency’s 1-30-04 approvable letter, including his review of the data pertinent to the question of dietary restrictions for the 20 mg patch. Dr. Dubitsky will also present his findings and arguments in favor of dietary restrictions at the October 26th meeting, and the sponsor will also present their arguments against having dietary restrictions. After you have heard all the findings and arguments, we will ask you to vote on two questions:

1. Do the available data for the Emsam 20 mg patch support the reasonable safety of this formulation without the need for dietary restrictions? **[Vote requested]**

[Background for Question #2: This question addresses the feasibility of having different requirements for dietary precautions for different patch strengths. Is it possible to adequately educate prescribers and patients about different dietary habits for different patch strengths, or would this be too confusing?]

2. If the Emsam 20 mg patch formulation could be considered reasonably safe for marketing without the need for dietary restrictions, would it be acceptable to market the 20 mg patch without dietary restrictions and at the same time require dietary restrictions for the 30 and 40 mg patch strengths? **[Vote requested]**

As for the questions for the first day, feel free to modify these questions, or add others that you think are relevant.

cc:
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