M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 3, 2014

FROM: Jing Zhang, MD. PhD.
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HFD-130

SUBJECT: Cross Discipline Team Leader Review

NDA/Supp#: 21336/S-010

Proprietary/ Established name: Emsam/Selegiline Transdermal System

Dosage forms/ Strength: 6, 9, or 12 mg/24 hours

Indication: Major Depressive Disorder (b) (4)

Recommendation: (b) (4)

I. Introduction and Background

Emsam is a transdermal patch formulation of selegiline, a non-selective, irreversible monoamine oxidase inhibitor (MAOI). Emsam is approved by FDA for the treatment of major depressive disorder in adults in doses of 6, 9, and 12 mg per 24 hours applied daily. Selegiline oral tablet or capsules in doses of 5 mg twice per day was approved for Parkinsonian patients who receive levodopa/carbidopa therapy and demonstrate a deteriorating response to the treatment.

Selegiline is a non-selective, irreversible MAOI. At antidepressant doses, it inhibits both monoamine oxidase A and B. Because selegiline has greater affinity for type B rather than then A activity. At recommended dose for treating Parkinson's disease, it can serve as a selective inhibitor of MAO-B.

In CNS neurons, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonin. MAOs are also important in the catabolism of various exogenous amines found in a variety of foods and drugs. MAO in the GI tract and liver (primarily type A), for example, is thought to provide vital

protection from exogenous amines (e.g., tyramine) that may cause a 'hypertensive crisis,' the so-called 'cheese reaction,' particularly when used in combination with other drugs that increase levels of catecholamines and serotonin, such as sympathomimetic agents and serotonergic antidepressants. Thus, the labeling of Emsam and other MAOI's contraindicate the concomitant use of several medications as well as advice to avoid consumption of food products with high tyramine content.

At the approval of Emsam for the treatment of MDD on February 27, 2006, FDA requested the sponsor to study the safety and efficacy of Emsam in children and adolescents ages 7 to 17 years as a post-marketing commitment. On May 15, 2006 the sponsor requested to waive the children study (7 to 11 years) because of a potential safety concern to study this population. The sponsor argued that children are more likely to achieve selegiline levels that need dietary tyramine restrictions at all Emsam strengths and the reliability of children in adhering to a diet restriction would be questionable. We agreed with the sponsor's argument and granted a partial waiver for 7 to 11 year age group on October 17, 2006.

On January 31, 2013, the sponsor submitted a Proposed Pediatric Study Request (PPSR) requesting that the Agency issue a Written Request (WR) for this completed trial. The Division felt that this PPSR was inadequate because (b) (4) Additional pediatric study is not necessary. The PeRC agreed with DPP's position in the meeting held on March 20, 2013, and an Inadequate Study Request letter was issued to the sponsor on April 4, 2013.

This supplement is intended to fulfill PMC and contains the study report of Study S9303-P0605—a double-blind, randomized, placebo-controlled, flexible dose, safety and efficacy trial in adolescents (12 to 17 years) with MDD. This study was conducted under IND 46,944.

II. Summary of Conclusions and Recommendations from Review Teams

1. CMC

There is no new CMC information submitted to this sNDA.

2. Nonclinical Pharmacology/Toxicology

There are no unresolved nonclinical pharmacology/toxicology issues for this application.

3. Clinical Pharmacology/Biopharmaceutics

There are no unresolved clinical pharmacology/biopharmaceutics issues for this application.

4. Clinical

Gregory Dubitsky, MD, is the primary medical reviewer for this submission. He did (b) (4) safety review of this submission. Please refer to his review for detailed safety review.

(b) (4)

(b) (4)

Safety:

In Dr. Dubitsky's review he concluded that safety data from trial S9303-P0605 revealed no new findings compared to the safety profile observed in adults except for an increased proportion of patients dropping out due to suicidal ideation in the Emsam group compared to placebo (2.6% versus 0.6%). An increased risk of suicidal ideation and behavior has been observed with other antidepressant drugs and class labeling of this risk has been implemented in Emsam labeling.

No deaths were reported in this trial. Ten patients experienced a nonfatal serious adverse event (SAE), 7 in the Emsam group and 3 in the placebo group. In Emsam group, reported SAEs were suicidal ideation (2 cases), agitation (2), orthostatic hypotension (1), gastritis (1) and uncontrollable screaming (1). Seventeen patients discontinued study drug treatment because of adverse events, 12 in Emsam treatment and 5 in placebo. Suicidal ideation is the most common AEs led to discontinuation.

Application site reactions were the most commonly reported adverse event (AE) in both treatment groups (24% in Emsam & 22% in placebo), and most of these cases were rated as mild. AEs that occurred >2% of patients and the rate was higher than placebo include application site reactions, insomnia, somnolence, vomiting, decreased appetite, agitation, anxiety, pharyngolaryngeal pain and upper respiratory tract infection.

No remarkable differences between Emsam and placebo were found in laboratory findings, vital sign changes, and ECGs.

5. OPDP

The Office of Prescription Drug Promotion (OPDP) conducted review of the sponsor proposed labels and made several recommendations that have been incorporated in the final product labeling.

6. OSI Inspection

No OSI inspection was requested because study S9303-P0605 was a negative study and no new safety findings were identified.

7. Labeling

Several revisions of physician labeling had been recommended by review divisions, OCP team, PMHS, OPDP, and the Patient Labeling Team (PLT)/the Office of Medical Policy Initiatives. We are still in the process negotiating the labeling with the sponsor. The final agreed upon labeling will be attached to the action letter when this NDA is taken action.

8. Pediatric Plan

A request to release the sponsor from PMC was presented to PeRC on Nov. 20, 2013. The committee agreed that the PMC has been met, and the safety data form the adolescent study should be incorporated in the product labeling.

9. Post Marketing Commitments or Requirements

No post marketing commitments are deemed necessary.

10. Risk Minimization Action Plan

No Risk Minimization Action Plan deemed necessary for this submission.

11. Conclusion and Recommendation

I agree with Dr. Dubitsky's conclusion that study S9303-P0605 dose fulfilled the PMC#1 (AP letter dated on Feb. 27, 2006, amended in Oct. 17, 2006)—required to assess the safety and effectiveness of Emsam as a treatment for MDD in adolescents ages 12 to 17.

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The safety profile of Emsam in adolescents remained same compared to that in adults.

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/s/

JING ZHANG
02/03/2014

MITCHELL V Mathis
02/03/2014
CR--label incomplete