

**Review and Evaluation of Clinical Data
NDA #21-336**

Sponsor: Somerset Pharmaceuticals
Drug: Emsam (selegiline transdermal system)
Indication: Major Depression
Material Reviewed: Resubmission: S-005 & S-010
Date Submitted: July 10, 2014
Date Received: July 10, 2014
DARRTS SDN: 377
Sequence Number: 0035

I. Background

Supplement S-005 to this NDA provided for the conversion of Emsam labeling to PLR format. Supplement S-010 contained the safety and efficacy data from a study of Emsam in adolescent patients (ages 12-17) with major depressive disorder (Study S9303-P0605). This trial was conducted to fulfill PMC #1 for this NDA.

These supplements were reviewed and a Complete Response (CR) letter was issued on February 3, 2014. Final approval of these supplements was contingent on the sponsor agreeing to the labeling changes contained in the CR letter.

The sponsor has now resubmitted these supplements with revised labeling. Because of a discrepancy between the cover letter and the draft labeling in this submission regarding contraindicated use in children under the age of 12 years, the sponsor submitted a corrected cover letter on July 28, 2014, at our request to clarify that they were in agreement with our request that Emsam be contraindicated in this age group.¹

The revised labeling is reviewed below.

II. Clinical Review of Revised Emsam Labeling

HIGHLIGHTS

CONTRAINDICATIONS

The sponsor agrees to the contraindication in children under 12 years old.

¹ The corrected cover letter was provided in eCTD sequence #0036 (DARRTS SDN 379) and was received by the Agency on July 28, 2014.

TABLE OF CONTENTS

The Table of Contents is acceptable.

FULL PRESCRIBING INFORMATION

CONTRAINDICATIONS (Section 4)

The sponsor agrees to the contraindication in children under 12 years old (b) (4)

WARNINGS AND PRECAUTIONS (Section 5)

Blood Pressure Elevation (5.3)

Tyramine-Induced Hypertensive Crisis

To avoid redundancy with the contraindications section, where it is more appropriately labeled, the sponsor proposes to remove the statement that Emsam is contraindicated in children under 12 years old because of an increased risk of hypertensive crisis.

USE IN SPECIFIC POPULATIONS (Section 8)

Pediatric Use (8.4)

As under contraindications, the sponsor agrees to the contraindication in children under 12 years old (b) (4)

. Also, they have added a statement that in patients under age 12, higher systemic exposure was observed compared to adolescents and they have added a reference to Clinical Pharmacology (Section 12.3), which presents some of these data.

CLINICAL PHARMACOLOGY (Section 12)

Pharmacokinetics (12.3)

Population Subgroups: Age

The sponsor has added pharmacokinetic data from study S9303-9814, which compared the pharmacokinetics of selegiline after 7 days of administration of a non-marketed 15mg/15cm² selegiline transdermal system in children (ages 6-11) and adolescents (ages 12-14). Mean trough plasma concentrations of selegiline in children (N=6) were higher than those in adolescents (N=4) (p=0.12): 2,562 pg/ml (SD=974) versus 1,821 pg/ml (SD=146), respectively.

PATIENT COUNSELING INFORMATION (Section 17)

How to Use Emsam

A statement has been added that detailed instructions are provided in the Medication Guide. Also added are detailed instructions for removing and disposing of patches at the end of the dosing interval (24 hours). These instructions are consistent with those in the approved Medication Guide for Daytrana (methylphenidate patch). (b) (4)

MEDICATION GUIDE

Instructions for Use

The sponsor has added detailed instructions for removal and disposal of the patch, consistent with the instructions added to Section 17.



III. Conclusions and Recommendations



Two reasons have been put forth to support a contraindication in patients under age 12: 1) children may have substantially higher plasma levels of selegiline than adolescents (and possibly adults) based on data from study S9303-P9814 and, therefore, children should follow a low tyramine diet at all Emsam strengths. This recommendation is different from that in adult patients and may be confusing to prescribers and patients, creating a hazard in children. 2) Children

² According to a July 21, 2014, Email from Ida-Lina Diak of the Division of Pharmacovigilance I, no reports consistent with hypertensive crisis in children treated with Emsam were found during searches of the FDA Adverse Event Reporting System (FAERS).

may not be intellectually capable of understanding and following a low tyramine diet. Nevertheless, the outcome of concern in either case is the same: a hypertensive crisis.

Accordingly, I suggest that the following statement be used to explain the contraindication in children under 12 years:


“EMSAM is contraindicated in patients less than 12 years of age because of the potential for a hypertensive crisis.”

It is recommended that this proposal be forwarded to the sponsor in an effort to reach agreement on labeling.

From a clinical standpoint, once agreement on labeling is reached and with the sponsor’s commitment to submit a Prior Approval labeling supplement to revise Section 17 and the Medication Guide as requested in our CR letter no later than September 30, 2014, these supplements may be approved.

IV. Proposed Comments to the Sponsor

We are reviewing your resubmission of NDA 21-336 S-010 and S-005 dated July 10, 2014, and amended on July 28, 2014. We acknowledge your agreement that EMSAM should be contraindicated in children under 12 years. (b) (4)



Two reasons have been put forth to support a contraindication in patients under age 12: 1) children may have substantially higher plasma levels of selegiline than adolescents based on data from study S9303-P9814 and, therefore, children should follow a low tyramine diet at all Emsam strengths. This recommendation is different from that in adult patients and may be confusing to prescribers and patients, creating a hazard in children. 2) Children may not be intellectually capable of understanding and following a low tyramine diet. Nevertheless, the outcome of concern in either case is the same: a hypertensive crisis.

Therefore, we would like to propose that the following statement be used to explain the contraindication in children under 12 years in Sections 4 and 8.4:

“EMSAM is contraindicated in patients less than 12 years of age because of the potential for a hypertensive crisis.”

Kindly inform us of the acceptability of this proposal at your earliest convenience and, if necessary, your counterproposal. Thank you in advance.

Gregory M. Dubitsky, M.D.
Medical Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GREGORY M DUBITSKY
08/01/2014

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08/01/2014