1 RECOMMENDATIONS/RISK-BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

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This submission does fulfill Postmarketing Commitment #1 under NDA 21-336 to study the safety and efficacy of Emsam in pediatric patients with major depressive disorder (MDD).

1.2 Risk-Benefit Assessment

Although the safety of Emsam in adolescent patients with MDD does not appear to be substantially different from that in adults with this disorder, the benefits of Emsam in this population have not been adequately demonstrated.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

There are no recommendations for a Risk Evaluation and Mitigation Strategy at this time.

1.4 Recommendations for Postmarketing Requirements and Commitments

No Postmarketing Requirements or Commitments are recommended.

2 INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Emsam is a transdermal patch containing the active ingredient selegiline, a monoamine oxidase inhibitor (MAOI). It is currently approved and marketed for the treatment of MDD in 6, 9, and 12mg/24 hrs patch strengths for once daily application. Due to a risk of hypertensive crisis with the two higher strength patches, patients using the 9mg/24 hrs and 12mg/24 hrs patches are required to adhere to a low tyramine diet.

2.2 Tables of Currently Available Treatments for Proposed Indications

Among the antidepressant agents approved by modern-day standards, only two are approved for use in adolescents with MDD: fluoxetine and escitalopram.

2.3 Availability of Proposed Active Ingredient in the United States

Selegiline is also available in the U.S. in oral tablets and capsules for the adjunctive treatment of patients with Parkinson's disease.

2.4 Important Issues With Consideration to Related Drugs

Selegiline is an irreversible inhibitor of monoamine oxidase and, at antidepressant doses, it inhibits both monoamine oxidase type A (MAO-A) and monoamine oxidase type B (MAO-B). This inhibition can produce elevations of adrenergic, serotonergic, and dopaminergic neurotransmitters, resulting in significant increases in blood pressure and serotonin syndrome, particularly when used in combination with other drugs that increase levels of these neurotransmitters, such as sympathomimetic agents and serotonergic antidepressants. Furthermore, the ingestion of foods and beverages with high tyramine content by patients taking MAOI's can produce severe hypertensive reactions via inhibition of tyramine metabolism by MAO in the gastrointestinal tract, leading to systemic absorption of excessive amounts of tyramine, which cause a sudden release of norepinephrine from neuronal storage sites. 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. Such contraindications must be exercised for at least two weeks after stopping MAOI's to allow regeneration of the MAO enzymes.

In addition, antidepressants are associated with an increased risk of suicidal ideation and behavior in children, adolescents, and young adults in short-term, placebo-controlled clinical trials.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Emsam was approved in the U.S. on February 27, 2006, for the treatment of MDD based on trials in adults. The approval carried a Postmarketing Commitment (PMC #1) to study the safety and efficacy of Emsam in children and adolescents (ages 7 to 17 years) with major depressive disorder (MDD) to fulfill requirements of the Pediatric Research Equity Act (PREA). We granted a waiver for studies in neonates and young children (ages 0 through 6 years).

On May 15, 2006, the sponsor requested a partial waiver of PREA requirements for children ages 7 to 11 years. The reason for this request was that children are likely to achieve selegiline levels that mandate dietary tyramine restrictions at all patch strengths and the reliability of children in adhering to a low tyramine diet

would be questionable, raising an important safety concern.[1] We agreed and, in a letter dated October 17, 2006, informed the sponsor that we had no objection to granting a partial waiver for the 7 to 11 year age group.

This supplement is intended to fulfill PMC #1 and contains the study report of an adequate, well-controlled safety and efficacy trial of Emsam in the treatment of adolescents (ages 12 through 17) with MDD (Study S9303-P0605). This trial was conducted under IND 46,944.

2.6 Other Relevant Background Information

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. It was the position of the Division of Psychiatry Products (DPP) that this PPSR was inadequate for the following reasons.

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Our position was presented to the Pediatric Review Committee (PeRC) on March 20, 2013. The PeRC agreed with DPP and an Inadequate Study Request letter was issued to the sponsor on April 4, 2013.

3 ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

Case report forms (CRF's) were submitted for 21 patients who participated in trial S9303-P0605 and are contained in Appendix 16.3.2 of the study report. I randomly selected a 10% sample (N=2) of these patients for auditing to determine if the adverse event information in the adverse event line listings (Listing 3.1 in Appendix 16.2) and the narrative summaries (Appendix 16.3.1)

[1] See my Review and Evaluation of Clinical Data under this NDA dated June 8, 2006, for a more detailed discussion of the partial waiver request.

was consistent with the information documented in the CRF's.[2] No inconsistencies across these three documents were identified.

3.2 Compliance with Good Clinical Practices

The sponsor certified that the submitted trial was conducted in compliance with Good Clinical Practice standards.

The sponsor certified that the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act were not used in any capacity in connection with trial S9303-P0605.[3]

3.3 Financial Disclosures

The sponsor provided the following information regarding the 26 sites in trial P9303-P0605:

- no investigators had disclosable information.
- no investigators had an employment relationship with the sponsor.
- in no case was the sponsor unable to obtain financial information.[4]

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Not applicable.

4.2 Clinical Microbiology

Not applicable.

4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted in this supplement.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of Emsam as an antidepressant is not fully understood but is presumed to be linked to potentiation of monoamine neurotransmitter activity in

[2] The following patients were selected: Center 30/Patient 342 and Center 25/Patient 148.
[3] Information was contained in a May 15, 2013, submission (eCTD Sequence 0026).
[4] Ibid.

the central nervous system produced by the inhibition of monoamine oxidase activity.

4.4.2 Pharmacodynamics

No new information on the pharmacodynamics of Emsam is included in this supplement.

4.4.3 Pharmacokinetics

In the pediatric (b) (4) trial submitted in this supplement (S9303-P0605), blood samples for pharmacokinetic analysis were obtained at screening and weeks 6 and 10. An attempt was made to obtain 2 or 3 blood samples over a period of 4 to 6 hours at weeks 6 and 10.

A number of samples assayed for metabolites were stored beyond the validated long-term stability period for the metabolite assay. These samples were excluded from the pharmacokinetic analysis.

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5 SOURCES OF CLINICAL DATA

5.1 Tables of Studies/Clinical Trials

Only one clinical trial forms the basis for this supplement: S9303-P0605 was a 12-week, randomized, double-blind, placebo-controlled, parallel group trial in 308 adolescents (ages 12 to 17 years) with major depressive disorder. Emsam was administered using a flexible dose strategy in the range 6 to 12 mg/24 hours.

5.2 Review Strategy

This review was based entirely on the clinical study report for trial S9303-P0605.

5.3 Discussion of Individual Studies/Clinical Trials

Data from trial S9303-P0605 formed the basis of this review. No Integrated Safety Summary or Integrated Summary of Efficacy was requested or submitted.

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7 REVIEW OF SAFETY

Safety Summary

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%). The overall reporting rate of suicidal ideation was the same in each group (2.6%). 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.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data in this supplement is derived solely from trial S9303-P0605.

7.1.2 Categorization of Adverse Events

I conducted a 100% audit of the sponsor's coding of reported adverse event terms to MedDRA Preferred Terms based on Listing 3.1 in Appendix 16.2 of the study report. No coding deficiencies were found.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This supplement is based on a single trial and, thus, no study pooling was possible.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

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7.2.4 Routine Clinical Testing

A systematic assessment of suicidal ideation and behavior, such as that using the Columbia-Suicide Severity Rating Scale (C-SSRS), was not performed in trial S9303-P0605. This assessment was based only reported adverse events. Nonetheless, class labeling regarding this risk has already been implemented for Emsam. Otherwise, clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No formal studies of drug metabolism or interactions were submitted in this supplement.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Routine monitoring of blood pressure was performed in this trial. Although the monitoring of suicidal ideation and attempts was not ideal, related adverse events were documented and analyzed in this trial and class labeling of this risk was implemented for Emsam.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in this trial.

7.3.2 Nonfatal Serious Adverse Events

A serious adverse event was defined in the trial protocol as any experience that was fatal, immediately life-threatening, produced persistent or significant disability or incapacity, required or prolonged hospitalization, or represented a congenital anomaly.

Ten patients experienced a nonfatal serious adverse event, 7 in the Emsam group and 3 in the placebo group. These patients and their events are listed in Table 5 below. Most were classified as serious because hospitalization was required. Six of these 10 patients dropped out due to the events.

Table 5: Patients with Serious Adverse Events

Patient #	Dropout?	SAE's
Emsam		
02-111	No	Gastritis, vomiting.
05-242	Yes	Suicidal ideation.
07-186	Yes	Suicidal ideation, anxiety.
12-078	Yes	Agitation.
23-195	No	Orthostatic hypotension, syncope.
23-307	Yes	Agitation.
30-342	Yes	Uncontrollable screaming.
Placebo		
16-173	No	Loss of consciousness, vomiting.
24-132	No	Mood swings.
30-296	Yes	Suicidal ideation.

Five cases merit further description and are summarized below.

Patient 02-111 was a 13 year old Black female who experienced vomiting on the day of her week 12 visit, causing her to miss the appointment. She had used Emsam 6mg/24 hrs. She was hospitalized the next day with an initial diagnosis of gastritis. Medical history was unremarkable. Concomitant medication consisted of birth control pills (Sprintec). There was no further information.

Patient 23-195 was a 17 year old Hispanic female using the 6mg/24 hr patch for about 5 weeks when she reported experiencing 3 syncopal episodes. Two days later, she had 2 more episodes and presented to the emergency room.

According to the patient's report, she was diagnosed with orthostatic hypotension, treated with intravenous fluids, and released. She continued in the trial. Her past medical history was remarkable for anemia, drug-induced hepatitis, seasonal allergies, and a rash on her forearms. Concomitant medication was Motrin.

Patient 30-342 was a 13 year old Black female treated with the 6mg/24 hr patch for 3 days when she locked herself in the apartment bathroom and began screaming uncontrollably. She was removed by security personnel and escorted to the hospital by police, where she was involuntarily admitted. On admission, she explained that she had a bad dream, woke up screaming, and had intrusive thoughts. She also was anxious. Study medication was stopped the next day and the blind was broken. The uncontrollable screaming lasted about one week. She was then discharged to the care of a legal guardian with prescriptions for Ativan and Risperdal to treat ongoing anxiety. There was no significant medical history.

Patient 16-173 was a 12 year old Caucasian male assigned to placebo who completed the study and 9 days later was hospitalized with severe vomiting and loss of consciousness. He was discharged the following day. He had a history of headaches and reflux. Concomitant medication during the trial consisted of Excedrin Migraine and Prilosec.

Patient 24-132 was a 14 year old Caucasian female treated with placebo who completed the study. About 3 weeks after her last dose, she experienced mood swings which worsened over the next few days and were marked by anger and irritability. She was hospitalized and treated with Seroquel and Zoloft. The mood swings resolved 4 days later and she was discharged. Her history was remarkable was acne and eczema.

Suicidal ideation was reported as a serious adverse event in 2 Emsam patients and one placebo patient. The reporting rate of all suicidal ideation (serious and non-serious) in this trial was 2.6% in each treatment arm. A systematic assessment of treatment-emergent suicidal ideation and behavior, such as with the Columbia-Suicide Severity Rating Scale, was not conducted in this trial. Emsam is currently labeled to describe a higher risk of suicidal thinking and behavior in children, adolescents, and young adults who are treated with antidepressant medications.

For two Emsam-treated patients and no placebo patients, agitation was reported as a serious adverse event. The reporting rate for all cases of agitation was slightly higher in Emsam patients than in placebo patients (3% and 2%, respectively). Also, agitation was a frequently reported adverse experience in Emsam premarketing trials in adults and, thus, does not represent a new safety signal, in my opinion.

The case of orthostatic hypotension and syncope in Patient 23-195 seems unlikely to be caused by Emsam for 2 reasons: 1) the onset occurred after 5 weeks of treatment with the 6mg/24 hr patch and 2) the patient remained in the study after the syncopal episodes, apparently with no recurrence.

In sum, examination of the serious adverse experiences in this trial reveals no new safety signals for Emsam in the pediatric population.

7.3.3 Dropouts Due to Adverse Events

Seventeen patients discontinued study drug treatment because of adverse events, including the 6 patients who dropped out due to serious adverse events listed in the previous section. The 11 dropouts due to non-serious adverse events are listed in Table 6 below.

Table 6: Patients Who Dropped Out Due To Adverse Events

Patient #	SAE's
Emsam	
05-346	Application site reaction.
11-040	Headache, mouth ulceration.
12-115	Suicidal ideation.
14-134	Nightmare.
15-073	Headache.
22-122	Suicidal ideation, depression.
28-205	Panic attack.
Placebo	
01-009	Migraine, abdominal discomfort.
04-003	Nausea, pyrexia, headache.
05-028	Rash
25-148	Depression, anxiety.

One patient dropped out due to an application site reaction, a very common occurrence with Emsam and placebo patches in adult trials: Patient 05-346 was a 17 year old Black female who developed a rash of moderate severity on her upper arm and right buttock, which were patch application sites, after receiving Emsam 6 mg/24 hrs for about 7 weeks. Emsam was stopped 2 days later and the reactions resolved about 2 weeks later.

In summary, there were no adverse events that led to dropout which are considered new safety signals.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Treatment-emergent adverse events that were reported in at least 2% of Emsam-treated patients and at a rate higher than in the placebo group are presented in Table 7 below.

Table 7: Reporting Rates of Treatment-Emergent Adverse Events

MedDRA System Organ Class/ Preferred Term	Emsam N=152	Placebo N=156
Gastrointestinal Disorders		
Toothache	2%	1%
Vomiting	5%	3%
Administration Site Disorders		
Application Site Reactions	24%	22%
Metabolism and Nutritional Disorders		
Decreased Appetite	3%	1%
Nervous System Disorders		
Somnolence	5%	3%
Postural Dizziness	2%	0%
Psychiatric Disorders		
Agitation	3%	2%
Anxiety	3%	1%
Insomnia	6%	3%
Respiratory Disorders		
Pharyngolaryngeal Pain	3%	2%
Upper Respiratory Tract Infection	7%	3%

By far, application site reactions were the most commonly reported adverse event and were reported slightly more frequently in the Emsam group (24% vs. 22% in placebo). Most application site reactions in both treatment groups were rated as mild and no reaction was rated as severe. Only one patient dropped out because of an application site reaction.

7.4.2 Laboratory Findings

An evaluation of the mean change from screening to end of study in hematology, serum chemistry, and urinalysis values revealed no substantial differences between the Emsam and placebo groups. Likewise, the proportion of changes from normal range at screening to outside normal range at the end of the study showed no remarkable differences between the treatment groups.

7.4.3 Vital Signs

Mean change from baseline to end of study in body temperature, respiratory rate, standing pulse and blood pressure, and orthostatic change in pulse and blood pressure demonstrated only small, unremarkable differences between treatment groups.

7.4.4 Electrocardiograms (ECG's)

ECG's were evaluated in terms of mean change from baseline in PR, QRS, and QT intervals (including Bazett's and Fridericia's corrections of the QT) as well as heart rate. There were no major differences between the Emsam and placebo treatment groups in these analyses.

Searches for QT interval outliers were conducted using the following criteria for both QTcB and QTcF:

- >450 msec (males) or >480 msec (females).
- >500 msec.
- >30 msec increase from baseline.
- >60 msec increase from baseline.

No patient had a corrected QT interval over 500msec. Regarding the other outlier analyses, the Emsam group was not substantially different from placebo.

8 POSTMARKETING EXPERIENCE

A cumulative review of postmarketing safety reports of hypertensive reactions with Emsam through December 12, 2012, was completed by the Division of Psychiatry Products Safety Team on March 4, 2013. This review was prompted by a data mining signal for "hypertensive crisis" discovered by the Office of Safety and Epidemiology Division of Pharmacovigilance I in early 2009. The DPP Safety Team review revealed no indication of a new hazard related to elevation in blood pressure but did show a substantial use of concomitant medication that could produce significant blood pressure increases. Some changes to Emsam labeling were recommended to clarify the information in labeling related to blood pressure elevation and serotonin syndrome. These recommendations will be considered during the PLR conversion of Emsam labeling.

9 APPENDICES

9.1 Literature Review/References

On June 10, 2013, I conducted the following two searches of the published literature for articles relevant to the safety of transdermal selegiline in children or

adolescents. One search utilized the PubMed database and the other used Embase.

PubMed
Search string = selegiline AND transdermal AND (children OR kids OR adolesc OR teenager OR pediatric). No date restrictions were implemented. This search produced 10 articles.

Embase
Drug = selegiline. Subheading = Adverse drug reaction. Route = transdermal. Dates = all years. Language = English. Age groups = ages 1-12 and 13-17. Two articles were produced.

None of the identified articles in either search described unexpected safety signals in pediatric patients treated with transdermal selegiline.

9.2 Labeling Recommendations

Although there were no significant safety findings in this trial which would require the addition of new safety information to labeling, it is recommended that the first paragraph in the Pediatric Use subsection of PRECAUTIONS in currently approved Emsam labeling be revised to advise prescribers that this trial was conducted and demonstrated no evidence of efficacy. Suggested language is shown below (added text is underlined).

Pediatric Use
Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS, Clinical Worsening and Suicide Risk**). (b) (4)

Finalization of the PLR conversion of Emsam labeling is planned during the review cycle for this supplement.

9.3 Advisory Committee Meeting

No advisory committee meeting was held with regard to this supplement.

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/s/

GREGORY M DUBITSKY
07/08/2013

JING ZHANG
07/08/2013