DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-336
NDA 21-708

Melissa L. Goodhead, B.S., RAC
Group Director, Regulatory Affairs/Quality Assurance
Somerset Pharmaceuticals, Inc.
2202 N. West Shore Blvd., Suite 450
Tampa, FL 33607

Dear Ms. Goodhead:

Please refer to your new drug application (NDA) 21-336, dated May 24, 2001, received May 25, 2001, and to your New Drug Application (NDA) 21-708, dated October 15, 2003, received October 16, 2003, both submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMSAM (selegiline transdermal system) patches, 6mg/24 hours, 9mg/24 hours, and 12mg/24 hours.

We acknowledge receipt of your additional submissions dated December 21, 2004, January 20, 2005, May 26, 2005, June 9, 2005, June 17, 2005, June 21, 2005, July 18, 2005, July 21, 2005, August 2, 2005, August 16, 2005, August 31, 2005, October 4, 2005, October 10, 2005, November 3, 2005, November 15, 2005, November 16, 2005, January 9, 2006, February 6, 2006, and February 7, 2006.

Your May 26, 2005 submission, received May 27, 2005, constituted a complete, Class 2 response to our January 30, 2004 action letter for both referenced NDAs. Additionally, your November 16, 2005, submission constituted an extension on the regulatory due date.

These new drug applications provide for the use of EMSAM (selegiline transdermal system) patches, 6mg/24 hours, 9mg/24 hours, and 12mg/24 hours in the acute (21-336) and longer-term (21-708) treatment of major depressive disorder in adult patients.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling and Medication Guide. Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved NDAs 21-336 & NDA 21-708**." Approval of these submissions by FDA is not required before the labeling is used.

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA, 21-336, for this drug product, not to NDA 21-708. In the future, do not make submissions to NDA 21-708 except for the final printed labeling requested above.

Pediatric Research Equity Act (PREA) Requirements-Studies Deferred
All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving studies for ages 0 to 7 years (neonates and young children). We are deferring submission of your pediatric studies for ages 7 to 17 years (children and adolescents) until July 30, 2009.

Pediatric Exclusivity
Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request" ***in addition to*** your plans for pediatric drug development described above. Please note that satisfaction of the requirements in Section 2 of PREA alone may not qualify you for pediatric exclusivity.

Dissolution Methods and Specifications
We note your agreement to accept the dissolution method and specifications requested for the dosage form. The agreed upon method and specification are presented here for reference:

Formulation(s)	**6mg/24 hours (20 mg / 20 cm^2) and (b)(4)**	**12mg/24 hours (40 mg / 40 cm^2)**
Media	(b)(4)	
Volume		
Temp (°C)		
Apparatus		
RPM		
Sampling Times And Specifications (% LC)		
Acceptance Criteria		

Phase 4 Commitments
We remind you of your postmarketing commitments agreed upon in communications dated May 26, 2005 and January 18, 2006. These commitments are listed below.

1. **Deferred pediatric studies under PREA**

   Your deferred pediatric study required under Section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of such postmarketing commitments shall be reported annually according to 21 CFR 314.81. The associated commitment is listed below.

   You are required to assess the safety and effectiveness of EMSAM as a treatment for Major Depressive Disorder in pediatric patients ages 7 to 17 (children and adolescents). Both children (ages 7 to 11) and adolescents (ages 12 to 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these age strata.

   Final Report Submission: July 30, 2009

   Please submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment, whether submitted to the IND or the NDA, must be clearly designated "**Required Pediatric Study Commitments**".

2. **Nonclinical Pharmacology and Toxicology: 2-year mouse carcinogenicity study (dermal route of application)**

   You are required to conduct a full 2-year carcinogenicity study of EMSAM in the mouse using the dermal route of application. Please refer to our action letter of January 30, 2004 for additional details regarding the need for this study. Please note that, as per the FDA Guidance "Special Protocol Assessment", the protocol for this study is eligible for special protocol review. Only one protocol at a time should be included in any submission for special protocol review, and each such protocol submitted should be submitted at least 90 days prior to the planned start of the study.

   Final Report Submission: July 30, 2009.

3. **Nonclinical Pharmacology and Toxicology: *in vivo* mouse micronucleus assay**

   You are required to conduct an *in vivo* mouse micronucleus assay either (a) via the oral route using a higher dose of selegiline in order to attain plasma exposures that cover the expected human plasma exposure or (b) via the dermal route. Please refer to our action letter of January 30, 2004 for additional details regarding the need for this study. Please note that, as per the FDA Guidance "Special Protocol Assessment", the protocol for this study is eligible for special protocol review. Only one protocol at a time should be included in any submission for special protocol review, each such protocol submitted should be submitted at least 90 days prior to the planned start of the study.

   Final Report Submission: July 30, 2007.

4. Clinical Pharmacology and Biopharmaceutics: *Adhesion*

Please provide information regarding the adhesion properties of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2), over a 3 week period under conditions approximating actual use. The following factors are to be examined in this study:

- Subject age [i.e., young healthy adults, the elderly (65 – 84 years old), and the extreme elderly (> 85)].
- Application to the different labeled application sites including the upper torso and upper arm.
- For each study arm 100 completers are anticipated.
- The data generated should be examined by gender, race, physical activity, bathing and showering practices. Therefore variations in each of these secondary factors should be well represented in each study arm.

Within 3 months of approval Somerset will submit the protocols for these studies and will submit the final study reports within 9 months following the agreement on the protocols.

5. Clinical Pharmacology and Biopharmaceutics: *Dermal Tolerability*

Please provide information regarding the dermal tolerability of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2), over a 3 week period under conditions approximating actual use. The following factors are to be examined in this study:

- Subject age [i.e. young healthy adults, the elderly (65 – 84 years old), and the extreme elderly (> 85)].
- Application to the different labeled application sites including the upper torso and upper arm.
- For each study arm 100 completers are anticipated.
- The data generated should be examined by gender, race, physical activity, bathing and showering practices. Therefore variations in each of these secondary factors should be well represented in each study arm.

Within 3 months of approval Somerset will submit the protocols for these studies and will submit the final study reports within 9 months following the agreement on the protocols.

6. Clinical Pharmacology and Biopharmaceutics: *Performance of Selegiline Transdermal Systems in the Elderly*

Only 3 subjects studied were > 65 years of age. All three were women and the eldest was 70 years old. Consequently, please provide information regarding the pharmacokinetic, pharmacodynamic and biopharmaceutic properties of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm^2 to 40 cm^2), in young healthy adults, the elderly (i.e. 65 – 84 y ears old), and the extreme elderly (i.e.> 85).

- The effects of gender and ethnicity/race should be examined for each age range.
- Information provided for each age group should include the following:
  - complete pharmacokinetic profiles of selegiline and the 3 metabolites previously examined
  - the tyramine response
  - MAO selectivity
  - drug delivery
  - safety information by age
- With regard to safety we are specifically interested in CNS effects, as well as differences in blood pressure changes, especially as the elderly typically have higher baseline systolic blood pressure and are at risk for orthostatic hypotension.

Within 3 months of approval Somerset will submit the protocols for these studies and will submit the final study reports within 9 months following the agreement on the protocols.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled

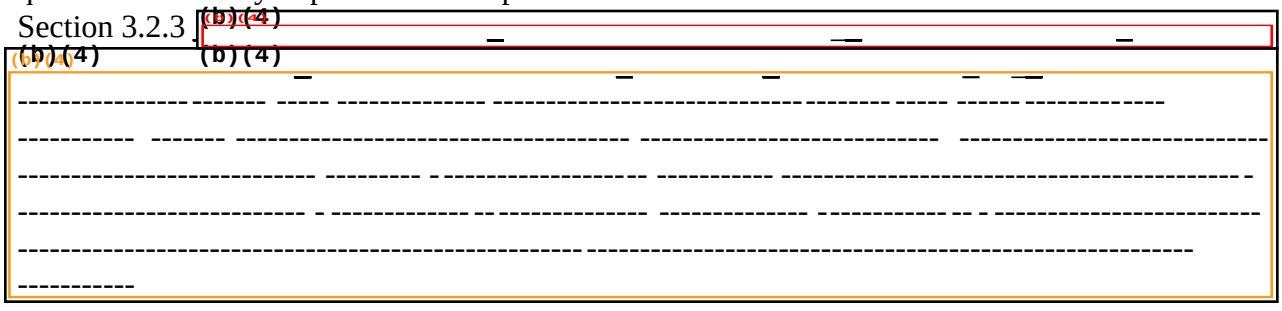
Comments and Recommendations on Risk Management Plan for EMSAM

Patient Education/Communication Tools (including the patient directed information to be placed on the unit-of-use packaging)

- The Medication Guide will be the main risk communication material for patients. All supplemental patient education pieces should reference the Medication Guide and/or contain identical language.
- A Wallet Card could be a useful tool; however, it may not be useful in its current form. There is a lot of information and the font size is quite small, and may not be readable for many patients. The font size of patient materials should be at least 10-point. The content should be limited to the concise key messages it is intended to convey, preferably in bulleted format.
- Since the prescriber will be responsible for the majority of the patient education, please ensure that prescribers are supplied with adequate teaching materials for their offices, including at minimum, the Wallet Card (with revisions as suggested above) and the Medication Guide.

Enhanced Pharmacovigilance Activities

- Section 3.2.1 'Spontaneous / Literature / Serious Clinical Trial Cases' (page # 12), mentions "creation of an algorithm to identify AEs of special interest related to hypertensive crisis and its complications". The algorithm was not included with this submission. Please submit the algorithm to the agency for possible comments.
- Section 3.2.2 'Targeted Adverse Event Follow-up' the RMP mentions that 'structured questionnaires will be designed to systematically collect targeted clinical and dietary intake information from spontaneous reports' of AEs of interest. Please submit to FDA the structured questionnaire that you plan to use for possible comments.
- Section 3.2.3 [redacted]



- Reporting of Postmarketing Adverse Events

- We ask that you submit hypertensive crisis reports of any dosage strength as expedited reports pending further evaluation.
- The RMP mentions that routine signal detection activities will occur on a monthly basis (as detailed in the November 21, 2005 submission). Please include a summary of this information as a section in the quarterly report.
- Please send a desk copy of the quarterly report, via the usual method of sending desk copies, marked for "ODS".

Specialized Unit-of-Use Packaging

- We agree that specialized unit-of-use packaging would be useful in helping to deliver the dietary modification message and is also the best way to ensure that the patient receives the MG.
- The **"Dietary Modifications Required"** term, which appears in red lettering in a red box on the packaging, may not be understandable for some patients. We suggest revising this language to make it clearer, e.g., "**Important: Do not eat certain foods while using Emsam (see enclosed Medication Guide)**.

Education and Outreach Monitoring

You plan to conduct both physician and patient tracking surveys to assess the education and outreach efforts and indicate and the results of such tracking will be reported to ODS at 9 and 15 month intervals following marketing. If physician and patient awareness of the primary risk communication message are below the pre-established goals for education and outreach, you indicate that you plan to create and implement a remediation plan to address deficiencies.

One of the patient tracking studies is described as a 2-wave quantitative survey among approximately 30 patients who received a prescription for Emsam, conducted at 6 and 12 months into the multi-layered education and outreach effort. The objective of the study will be to measure the percentage of patients receiving written information about Emsam risk management, the usefulness of patient materials received and the awareness of the key risk management messages. Please submit your complete protocol, when available, for further review and comment.

Comments and Recommendations on Container, Carton, and Patch Labeling

GENERAL COMMENTS

- The total drug amount per patch size (XX mg/XX cm^2) may immediately follow the expression of strength per 24 hours or be located on the side panel for further clarification. If the total drug content per patch size will immediately follow the expression of strength per 24 hours, the total drug content per patch size should be given less prominence in order to avoid confusion.

- You have placed the statement "Dietary Modification Required" on the 9 mg/24 hours and 12 mg/24 hours container labels and carton labeling.

    - This statement should refer to the MedGuide where it is further defined.

- We are concerned that patients may double up with the 6 mg/24 hours patch for a 12 mg/24 hours dose yet not follow or be aware of the dietary restrictions since this strength is not labeled as such. To remedy this situation, we suggest that all packaging materials for the 6 mg/24 hours patch remind patients not to wear more than 1 patch at a time.

CONTAINER LABEL (Pouch)

- See GENERAL COMMENTS above

- The established name is difficult to read due to elongated font style and inadequate spacing between the letters. Please revise to increase the readability of the established name.

- The unit designation (i.e. mg, cm^2, and h) immediately follows the numbers without a space. Insert a space between the number and unit designation to improve readability.

- Relocate the expression of strength to follow the established name where it appears on each principal display panel.

- The pictorials on the back of the container label show a man wearing multiple patches. While DMETS realizes the intent of this pictorial is to show different proper sites for patch adhesion, it could be misinterpreted as a direction to place multiple patches on. DMETS prefers that arrows be used and that a tile accompany the pictorial.

- The white writing on grey background for the 12 mg/24 hours strength is difficult to read. Please increase the background contrast by darkening the grey background.

- Include lot number and expiration date on the pouch label.

PATCH LABEL

- We acknowledge comments that your patch will have a "clear backer". Reports in the literature describe cases of multiple patches being applied to hospitalized patients because of overlooked clear or translucent patches[1]. To prevent adhesion of multiple patches, DMETS encourages use of visual cues, i.e., name and strength, such that old patches can be easily found for removal and are not overlooked. Additionally, consideration should be given to revising the patch so it has color. We acknowledge your comments that the patch label will be printed with white ink on a clear backer and that the black background represented by draft labeling is for viewing purposed only. Please ensure that there is sufficient contrast to afford adequate readability for the actual product once placed on the patient's body.

[1] Institute for Safe Medication Practices Press Release: ISMP calls for more action to safeguard pain patches. August 13, 2005.

- We encourage the use of colors, boxing or some other means to differentiate the different strengths of the patches.

- Allow the established name to follow the proprietary name on the patch. We refer you to 21 CFR 201.10(g)(1) for guidance.

CARTON LABELING

- See GENERAL COMMENTS

PACKAGE INSERT LABELING

- See GENERAL COMMENTS

- HOW SUPPLIED

  Include the established name of the drug product in association with the proprietary name where it appears in this section.

In addition, submit three copies of the introductory promotional materials that you propose to use for this/these product(s). Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Psychiatry Products and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Renmeet Gujral, Pharm.D., Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Labeling and Medguide

EMSAM®
(SELEGILINE TRANSDERMAL SYSTEM)
CONTINUOUS DELIVERY FOR ONCE-DAILY APPLICATION

Rx only

Suicidality in Children and Adolescents

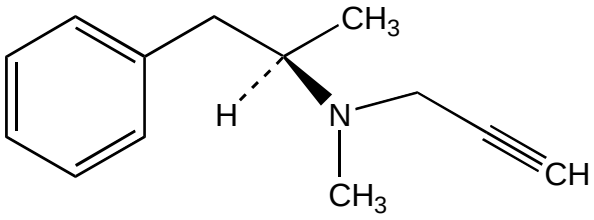
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of EMSAM or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised for the need for close observation and communication with the prescriber. EMSAM is not approved for use in pediatric patients. (See WARNINGS and PRECAUTIONS, Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRI's and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

DESCRIPTION

EMSAM® (selegiline transdermal system) is a transdermally administered antidepressant. When applied to intact skin, **EMSAM** is designed to continuously deliver selegiline over a 24-hour period.

Selegiline base is a colorless to yellow liquid, chemically described as (-)-(*N*)-Methyl-*N*-[(1*R*)-1-methyl-2-phenylethyl]prop-2-yn-1-amine. It has an empirical formula of $C_{13}H_{17}N$ and a molecular weight of 187.30. The structural formula is:

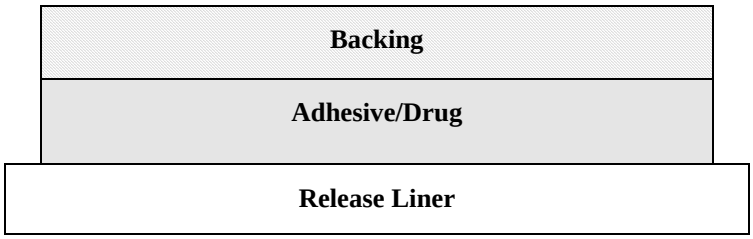


Selegiline Base

EMSAM systems are transdermal patches that contain 1 mg of selegiline per cm^2 and deliver approximately 0.3 mg of selegiline per cm^2 over 24 hours. **EMSAM** systems are available in three sizes: $20mg/20cm^2$, $30mg/30cm^2$, and $40mg/40cm^2$ that deliver, on average, doses of 6mg, 9mg or 12mg, respectively, of selegiline over 24 hours.

EMSAM is a matrix-type transdermal system composed of three layers as illustrated in Figure 1 below. Layer 1 is the Backing Film that provides the matrix system with occlusivity and physical integrity and protects the adhesive/drug layer. Layer 2 is the Adhesive/Drug Layer. Layer 3 consists of side-by-side release liners that are peeled off and discarded by the patient prior to applying **EMSAM**. The inactive ingredients are acrylic adhesive, ethylene vinyl acetate/polyethylene, polyester, polyurethane, and silicon coated polyester.

Figure 1: Side view of EMSAM system. (Not to scale).



CLINICAL PHARMACOLOGY

Pharmacodynamics

Selegiline (the drug substance of **EMSAM**) is an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. MAO exists as two isoenzymes, referred to as MAO-A and MAO-B. Selegiline has a greater affinity for MAO-B, compared to MAO-A. However, at antidepressant doses, selegiline inhibits both isoenzymes (see below).

The mechanism of action of EMSAM as an antidepressant is not fully understood, but is presumed to be linked to potentiation of monoamine neurotransmitter activity in the central nervous system (CNS) resulting from its inhibition of MAO activity. In an *in vivo* animal model used to test for antidepressant activity (Forced Swim Test), selegiline administered by transdermal patch exhibited antidepressant properties only at doses that inhibited both MAO-A and MAO-B activity in brain. In the CNS, MAO-A and MAO-B play important roles in the catabolism of neurotransmitter amines such as norepinephrine, dopamine, and serotonin, as well as neuromodulators such as phenylethylamine. Other molecular sites of action have also been explored and in this regard, a direct pharmacological interaction may also occur between selegiline and brain neuronal α_{2B} receptors. In *in vitro* receptor binding assays, selegiline has demonstrated affinity for the human recombinant adrenergic α_{2B} receptor (K_i = 284 nM). No affinity [K_i >10 μM] was noted at dopamine receptors, adrenergic β_3, glutamate, muscarinic M_1-M_5, nicotinic, or rolipram receptor/sites.

Pharmacokinetics

<u>Absorption</u>

Following dermal application of **EMSAM** to humans, 25% - 30% of the selegiline content on average is delivered systemically over 24 hours, (range ~ 10% - 40%). Consequently, the degree of drug absorption may be 1/3 higher than the average amounts of 6 to 12mg per 24 hours. Transdermal dosing results in substantially higher exposure to selegiline and lower exposure to metabolites compared to oral dosing, where extensive first-pass metabolism occurs (Figure 2). In a 10-day study with **EMSAM** administered to normal volunteers, steady-state selegiline plasma concentrations were achieved within five days of daily dosing. Absorption of selegiline is similar when EMSAM is applied to the upper torso or upper thigh. Mean (95% CI) steady-state plasma concentrations in healthy men and women following application of **EMSAM** to the upper torso or upper thigh are shown in Figure 3.

Figure 2: Average AUC_{inf} (ng·hr/mL) of selegiline and the three major metabolites estimated for a single, 24-hour application of an EMSAM 6mg/24hours Patch and a single, 10mg oral immediate release dose of selegiline HCl in 12 healthy male and female volunteers

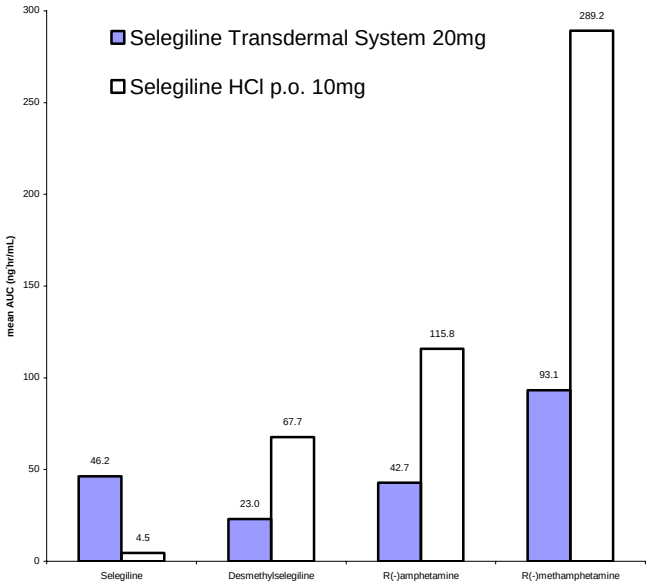


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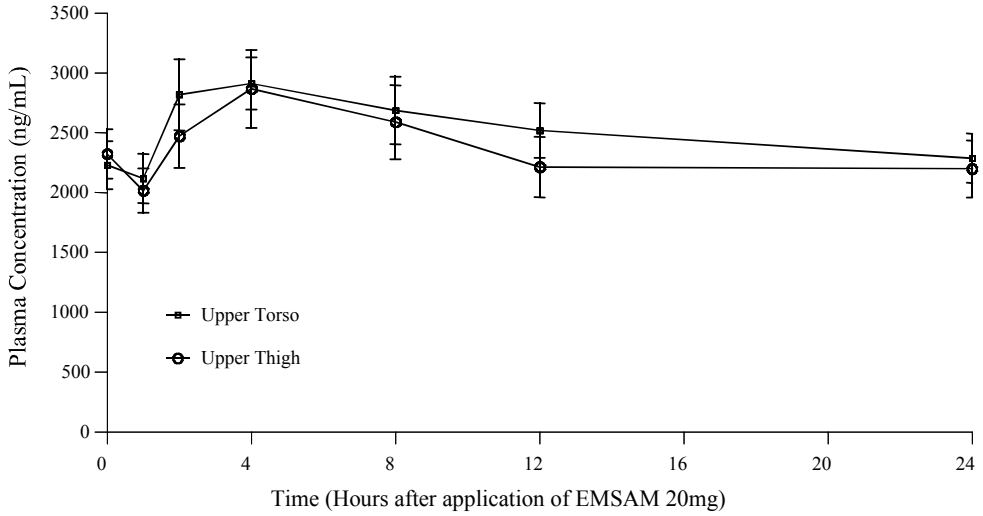
Figure 3. Average plasma (±95% CI) selegiline concentrations in healthy male and female volunteers at steady-state after application of EMSAM 6mg/24 hours to the upper torso.



Distribution

Following dermal application of radiolabeled selegiline to laboratory animals, selegiline is rapidly distributed to all body tissues. Selegiline rapidly penetrates the blood-brain barrier.

In humans, selegiline is approximately 90% bound to plasma protein over a 2-500 ng/mL concentration range. Selegiline does not accumulate in the skin.

In vivo Metabolism

Transdermally absorbed selegiline (via **EMSAM**) is not metabolized in human skin and does not undergo extensive first-pass metabolism. Selegiline is extensively metabolized by several CYP_{450}-dependent enzyme systems (**see *In vitro* Metabolism**). Selegiline is metabolized initially via N-dealkylation or N-depropargylation to form N-desmethylselegiline or R-(-) methamphetamine, respectively. Both of these metabolites can be further metabolized to R-(-)amphetamine. These metabolites are all levorotatory (l-) enantiomers and no racemic biotransformation to the dextrorotatory form (i.e., S(+)-amphetamine or S(+)-methamphetamine) occurs. R(-)-methamphetamine and R(-)-amphetamine are mainly excreted unchanged in urine.

In vitro Metabolism

In vitro studies utilizing human liver microsomes demonstrated that several CYP_{450}-dependent enzymes are involved in the metabolism of selegiline and its metabolites. CYP2B6, CYP2C9, and CYP3A4/5 appeared to be the major contributing enzymes in the formation of R(-)-methamphetamine from selegiline, with CYP2A6 having a minor role. CYP2A6, CYP2B6, and CYP3A4/5 appeared to contribute to the formation of R(-)-amphetamine from N-desmethylselegiline.

The potential for selegiline or N-desmethylselegiline to inhibit individual CYP_{450}-dependent enzyme pathways was also examined *in vitro* with human liver microsomes. Each substrate was examined over

a concentration range of 2.5 to 250 μM. Consistent with competitive inhibition, both selegiline and N-desmethylselegiline caused a concentration dependent inhibition of CYP2D6 at 10 – 250 μM and CYP3A4/5 at 25 - 250 μM. CYP2C19 and CYP2B6 were also inhibited at concentrations ≥ 100 μM. All inhibitory effects of selegiline and N-desmethylselegiline occurred at concentrations that are several orders of magnitude higher than concentrations seen clinically (highest predose concentration observed at a dose of 12mg/24hours at steady-state was 0.046 μM) (see **PRECAUTIONS, Drug Interactions**).

Excretion

Approximately 10% and 2% of a radiolabeled dose applied dermally, as a DMSO solution, was recovered in urine and feces respectively, with at least 63% of the dose remaining unabsorbed. The remaining 25% of the dose was unaccounted for. Urinary excretion of unchanged selegiline accounted for 0.1% of the applied dose with the remainder of the dose recovered in urine being metabolites.

The systemic clearance of selegiline after intravenous administration was 1.4 L/min, and the mean half-lives of selegiline and its three metabolites, R(-)-N-desmethylselegiline, R(-)- amphetamine, and R(-)-methamphetamine, ranged from 18 - 25 hours.

Population Subgroups

Age—The effect of age on the pharmacokinetics or metabolism of selegiline during administration of **EMSAM** has not been systematically evaluated. The recommended dose for elderly patients is **EMSAM** 6mg/24hours. (See **DOSAGE AND ADMINISTRATION**.)

Gender--No gender differences have been observed in the pharmacokinetics or metabolism of selegiline during administration of **EMSAM**. No adjustment of **EMSAM** dosage based on gender is needed.

Reduced Hepatic Function

After a single administration of EMSAM 6mg/24hours in 8 patients with mild or moderate liver impairment (Child-Pugh classifications of A or B), no differences in either the metabolism or pharmacokinetic behavior of selegiline or its metabolites were observed as compared with data of normal subjects. No adjustment of EMSAM dosage is required in patients with moderate liver impairment.

Reduced Renal Function

Data from a single dose study examining the pharmacokinetics of EMSAM 6mg/24hours in 12 patients with renal impairment suggest that mild, moderate, or severe renal impairment does not affect the pharmacokinetics of selegiline after transdermal application. Therefore, no adjustment of EMSAM dosage is required in patients with renal impairment.

Dermal Adhesion

Dermal adhesion of EMSAM was examined after application of 6mg/24hours selegiline patches for 10 days to the upper-torso. Approximately 88% - 89% of 6mg/24hours selegiline patches applied to the upper torso exhibited <10% lift with approximately 6 – 7 % of patches becoming detached.

External Heat

The effect of direct heat applied to the EMSAM patch on the bioavailability of selegiline has not been studied. However, in theory, heat may result in an increase in the amount of selegiline absorbed from the EMSAM patch and produce elevated serum levels of selegiline. Patients should be advised to avoid exposing the EMSAM application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Clinical Efficacy Trials

The efficacy of **EMSAM** as a treatment for major depressive disorder was established in two placebo-controlled studies of six and eight weeks duration in adult outpatients (ages 18 to 70 years) meeting DSM-IV criteria for major depressive disorder. In both studies, patients were randomized to double-blind treatment with **EMSAM** or placebo. The 6-week trial (N=176) showed that **EMSAM** 6mg/24hours was significantly more effective than placebo on the 17-item Hamilton Depression Rating Scale (HAM-D). In an 8-week dose titration trial, depressed patients (N=265), who received **EMSAM** or placebo at a starting dose of 6mg/24hours, with possible increases to 9mg/24hours or 12mg/24hours based on clinical response, showed significant improvement compared with placebo on the primary outcome measure, the 28-item HAM-D total score.

In another trial, 322 patients meeting DSM-IV criteria for major depressive disorder who had responded during an initial 10-week open-label treatment phase for about 25 days, on average, to **EMSAM** 6mg/24hours, were randomized either to continuation of **EMSAM** at the same dose (N=159) or to placebo (N=163) under double-blind conditions for observation of relapse. About 52% of the **EMSAM**-treated patients, as well as about 52% of the placebo-treated patients, had discontinued treatment by week 12 of the double-blind phase. Response during the open-label phase was defined as 17-item HAM-D score <10 at either week 8 or 9 and at week 10 of the open-label phase. Relapse during the double-blind phase was defined as follows : (1) a 17-item HAM-D score ≥ 14, (2) a CGI-S score of ≥ 3 (with at least a 2-point increase from double-blind baseline), and (3) meeting DSM-IV criteria for major depressive disorder on two consecutive visits ≥ 11 days apart. In the double-blind phase, patients receiving continued **EMSAM** experienced a significantly longer time to relapse.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

INDICATIONS AND USAGE

EMSAM is indicated for the treatment of major depressive disorder.

The efficacy of **EMSAM** in the treatment of major depressive disorder was established in 6- and 8-week placebo-controlled trials of outpatients with diagnoses of DSM-IV category of major depressive disorder (see **Clinical Efficacy Trials**).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicide attempt or suicidal ideation.

The benefit of maintaining patients with major depressive disorder on therapy with **EMSAM** after achieving a responder status for an average duration of about 25 days was demonstrated in a controlled

trial (see **Clinical Efficacy Trials** under **CLINICAL PHARMACOLOGY**). The physician who elects to use **EMSAM** for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

The antidepressant action of **EMSAM** in hospitalized depressed patients has not been studied.

CONTRAINDICATIONS

EMSAM is contraindicated in patients with known hypersensivity to selegiline or to any component of the transdermal system.

EMSAM is contraindicated with selective serotonin re-uptake inhibitors (SSRI's, e.g., fluoxetine, sertraline, and paroxetine), dual serotonin and norepinephrine re-uptake inhibitors (SNRI's, e.g., venlafaxine and duloxetine), tricyclic antidepressants (TCA's, e.g., imipramine and amitripyline), bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone and propoxyphene; the antitussive agent dextromethorphan; St. John's wort; mirtazapine; and cyclobenzaprine. EMSAM should not be used with oral selegiline or other MAO inhibitors (MAOI's e.g., isocarboxazid, phenelzine, and tranylcypromine) (see **WARNINGS**).

Carbamazepine and oxcarbazepine are contraindicated in patients taking selegiline. (see **PRECAUTIONS, Drug Interactions**).

As with other MAOI's, **EMSAM** is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine).

As with other MAOI's, patients taking **EMSAM** should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. EMSAM should be discontinued at least 10 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously.

As with other MAOI's, **EMSAM** is contraindicated for use in patients with pheochromocytoma.

EMSAM is an irreversible MAO inhibitor. As a class, these compounds have been associated with hypertensive crises caused by the ingestion of foods containing high amounts of tyramine. In its entirety, the data for **EMSAM** 6mg/24hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9mg/24hours and 12mg/24hours, patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9mg/24hours and 12mg/24hours**. (See **WARNINGS and PRECAUTIONS, Drug Interactions, Tyramine**.)

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes

in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disoders.

Pooled analyses of short-term placebo-controlled trials of nine antidepressant drugs (SSRI's and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms.

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted

about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and care givers. Prescriptions for **EMSAM** should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that **EMSAM** is not approved for use in treating bipolar depression.

Hypertensive Crisis

EMSAM is an irreversible MAO inhibitor. MAO is important in the catabolism of dietary amines (e.g., tyramine). In this regard, significant inhibition of intestinal MAO-A activity can impose a cardiovascular safety risk following the ingestion of tyramine-rich foods. As a class, MAOI's have been associated with hypertensive crises caused by the ingestion of foods with a high concentration of tyramine. Hypertensive crises, which in some cases may be fatal, are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain. Intracranial bleeding has been reported in association with the increase in blood pressure. Patients should be instructed as to the signs and symptoms of severe hypertension and advised to seek immediate medical attention if these signs or symptoms are present.

In 6 of the 7 clinical studies conducted with **EMSAM** at doses of 6mg/24hours-12mg/24hours, patients were not limited to a modified diet typically associated with this class of compounds. Although no hypertensive crises were reported as part of the safety assessment, the likelihood of developing this reaction cannot be fully determined since the amount of tyramine typically consumed during the course of treatment is not known and blood pressure was not continuously monitored.

To further define the likelihood of hypertensive crises with use of EMSAM, several Phase I tyramine challenge studies were conducted both with and without food (see PRECAUTIONS, Drug Interactions, Tyramine). In its entirety, the data for EMSAM 6mg/24hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for EMSAM 9mg/24hours, and the results from the Phase I tyramine challenge study in fed volunteers administered EMSAM 12mg/24hours (See **PRECAUTIONS**, **Drug Interactions**, Tyramine), patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9mg/24hours and 12mg/24hours**.

If a hypertensive crisis occurs, **EMSAM** should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. Phentolamine 5mg or labetalol 20mg administered slowly intravenously is recommended therapy to control hypertension. Alternately, nitroprusside

delivered by continuous intravenous infusion may be used. Fever should be managed by means of external cooling. Patients must be closely monitored until symptoms have stabilized.

Dietary Modifications Required for Patients Taking EMSAM 9mg/24hours and 12mg/24hours

The following foods and beverages should be avoided beginning on the first day of **EMSAM** 9mg/24hours or 12mg/24hours treatment and should continue to be avoided for two weeks after a dose reduction to EMSAM 6mg/24hours or following the discontinuation of **EMSAM** 9mg/24hours or 12mg/24hours.

Food and beverages to avoid and those which are acceptable[1]:

Class of Food and Beverage	Tyramine-Rich Foods and Beverages to Avoid	Acceptable Foods, Containing No or Little Tyramine
Meat, Poultry and Fish	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring; and any spoiled or improperly stored meat, poultry and fish (e.g., foods that have undergone changes in coloration, odor, or become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry and fish, including fresh processed meats (e.g., lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese and yogurt
Beverages	All varieties of tap beer, and beers that have not been pasteurized so as to allow for ongoing fermentation	As with other antidepressants, concomitant use of alcohol with **EMSAM** is not recommended. (Bottled and canned beers and wines contain little or no tyramine)
Miscellaneous	Concentrated yeast extract (e.g., Marmite), sauerkraut, most soybean products (including soy sauce and tofu); OTC supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain-restaurant pizzas prepared with cheeses low in tyramine

[1] Adapted from K. I. Shulman, S. E. Walker, Psychiatric Annals 2001; 31:378-384

Use With Other Drugs Affecting Monoamine Activity

Serious, sometimes fatal, central nervous system (CNS) toxicity referred to as the "serotonin syndrome" has been reported with the combination of non-selective MAOI's with certain other drugs, including

tricyclic or selective serotonin reuptake inhibitor antidepressants, amphetamines, meperidine, or pentazocine. Serotonin syndrome is characterized by signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Similar less severe syndromes have been reported in a few patients receiving a combination of oral selegiline with one of these agents.

Therefore, **EMSAM** should not be used in combination with selective serotonin reuptake inhibitors (SSRI's, e.g., fluoxetine, sertraline, paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRI's, e.g., venlafaxine and duloxetine); tricyclic antidepressants (TCA's, e.g., imipramine and amitripyline); oral selegiline or other MAOI's (e.g., isocarboxazid, phenelzine, and tranylcypromine), mirtazapine; bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone, and propoxyphene; the antitussive agent dextromethorphan, or St. John's wort because of the risk of life-threatening adverse reactions. Also, **EMSAM** should not be used with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine). (see **CONTRAINDICATIONS**).

Concomitant use of **EMSAM** with buspirone hydrochloride is not advised since several cases of elevated blood pressure have been reported in patients taking MAO inhibitors who were then given buspirone HCl.

After stopping treatment with SSRI's, SNRI's, TCA's, MAOI's, meperidine and analgesics such as tramadol, methadone, and propoxyphene; dextromethorphan, St. John's wort, mirtazapine, bupropion HCl, or buspirone HCl, a time period equal to 4-5 half lives (approximately 1 week) of the drug or any active metabolite should elapse before starting therapy with **EMSAM**. Because of the long half-life of fluoxetine and its active metabolite, at least five weeks should elapse between discontinuation of fluoxetine and initiation of treatment with **EMSAM**. At least two weeks should elapse after stopping **EMSAM** before starting therapy with buspirone HCl or a drug that is contraindicated with **EMSAM**.

PRECAUTIONS

General

Hypotension

As with other MAOI's, postural hypotension, sometimes with orthostatic symptoms, can occur with **EMSAM** therapy. In short-term, placebo-controlled depression studies, the incidence of orthostatic hypotension (i.e., a decrease of 10mmHg or greater in mean blood pressure when changing position from supine or sitting to standing) was 9.8% in EMSAM-treated patients and 6.7% in placebo-treated patients. It is recommended that elderly patients treated with **EMSAM** be closely observed for postural changes in blood pressure throughout treatment. Dose increases should be made cautiously in patients with pre-existing orthostasis. Postural hypotension may be relieved by having the patient recline until the symptoms have abated. Patients should be cautioned to change positions gradually. Patients displaying orthostatic symptoms should have appropriate dosage adjustments as warranted.

Activation of Mania/Hypomania

During Phase III trials, a manic reaction occurred in 8/2036 (0.4%) patients treated with **EMSAM**. Activation of mania/hypomania can occur in a small proportion of patients with major affective disorder treated with other marketed antidepressants. As with all antidepressants, **EMSAM** should be used cautiously in patients with a history of mania.

Use in Patients With Concomitant Illness

Clinical experience with **EMSAM** in patients with certain concomitant systemic illnesses is limited. Caution is advised when using **EMSAM** in patients with disorders or conditions that can produce altered metabolism or hemodynamic responses.

EMSAM has not been systematically evaluated in patients with a history of recent myocardial infarction or unstable heart disease. Such patients were generally excluded from clinical studies during the product's premarketing testing.

No ECG abnormalities attributable to **EMSAM** were observed in clinical trials.

Although studies of phenylpropanolamine and pseudoephedrine did not reveal pharmacokinetic drug interactions with **EMSAM**, it is prudent to avoid the concomitant use of sympathomimetic agents, such as some decongestants.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with **EMSAM** and should counsel them in its appropriate use. A patient Medication Guide about Using Antidepressants in Children and Teenagers is available for **EMSAM**. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking **EMSAM**.

Clinical Worsening and Suicide Risk:

Patients, their families and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment or when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly change in the medication.

General

Patients should be advised not to use oral selegiline while on **EMSAM** therapy.

Patients should be advised not to use carbamazepine or oxcarbamazepine while on **EMSAM** therapy.

Patients should be advised not to use meperidine and analgesic agents such as tramadol, methadone, and propoxyphene.

Patients should be advised not to use sympathomimetic agents while on **EMSAM** therapy.

Patients should be advised not to use selective serotonin reuptake inhibitors (SSRI's, e.g., fluoxetine, sertraline, paroxetine, and St. John's wort), dual serotonin and norepinephrine reuptake inhibitors (SNRI's, e.g., venlafaxine and duloxetine), tricyclic antidepressants (TCA's, e.g., imipramine and amitripyline), mirtazapine, oral selegiline or other MAOI's (e.g., isocarboxazid, phenelzine, and tranylcypromine), bupropion hydrochloride or buspirone hydrochloride while on **EMSAM** therapy.

EMSAM has not been shown to impair psychomotor performance; however, any psychoactive drug may potentially impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that **EMSAM** therapy does not impair their ability to engage in such activities.

Patients should be told that, although **EMSAM** has not been shown to increase the impairment of mental and motor skills caused by alcohol, the concomitant use of **EMSAM** and alcohol in depressed patients is not recommended.

Patients should be advised to notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbals, because of the potential for drug interactions. Patients should also be advised to avoid tyramine-containing nutritional supplements and any cough medicine containing dextromethorphan.

Patients should be advised to use **EMSAM** exactly as prescribed. The need for dietary modifications at higher doses should be explained, and a brief description of hypertensive crisis provided. Rare hypertensive reactions with oral selegiline at doses recommended for Parkinson's disease and associated with dietary influences have been reported. The clinical relevance to **EMSAM** is unknown.

Patients should be advised that certain tyramine rich foods and beverages should be avoided while on **EMSAM** 9mg/24hours or **EMSAM** 12mg/24hours, and for two weeks following discontinuation of **EMSAM** at these doses (See **CONTRAINDICATIONS** and **WARNINGS**).

Patients should be instructed to immediately report the occurrence of the following acute symptoms: severe headache, neck stiffness, heart racing or palpitations, or other sudden or unusual symptoms.

Patients should be advised to avoid exposing the EMSAM application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight since heat may result in an increase in the amount of selegiline absorbed from the EMSAM patch and produce elevated serum levels of selegiline.

Patients should be advised to change position gradually if lightheaded, faint, or dizzy while on **EMSAM** therapy.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast-feeding an infant.

While patients may notice improvement with **EMSAM** therapy in one to several weeks, they should be advised of the importance of continuing drug treatment as directed.

Patients should be advised not to cut the **EMSAM** system into smaller portions.

For instructions on how to use **EMSAM**, see **DOSAGE AND ADMINISTRATION, How to Use EMSAM**.

Drug Interactions

The potential for drug interactions between **EMSAM** and a variety of drugs was examined in several human studies. Drug interaction studies described below were conducted with **EMSAM** 6mg/24hours. Although no differences are expected, drug interaction studies have not been conducted at higher doses (see ***In vitro* Metabolism**). In all of the studies described below, no drug-related adverse events were noted that required discontinuation of any subjects. Further, the incidence and nature of the adverse events were consistent with those known for selegiline or the test agent.

Alcohol

The pharmacokinetics and pharmacodynamics of alcohol (0.75 mg/kg) alone or in combination with **EMSAM** 6mg/24hours for 7 days of treatment was examined in 16 healthy volunteers. No clinically significant differences were observed in the pharmacokinetics or pharmacodynamics of alcohol or the pharmacokinetics of selegiline during co- administration. Although **EMSAM** has not been shown to increase the impairment of mental and motor skills caused by alcohol (0.75 mg/kg) and failed to alter the pharmacokinetic properties of alcohol, patients should be advised that the use of alcohol is not recommended while taking **EMSAM**.

Alprazolam

In subjects who had received **EMSAM** 6mg/24hours for 7 days, co-administration with alprazolam (15 mg/day), a CYP3A4/5 substrate, did not affect the pharmacokinetics of either selegiline or alprazolam.

Carbamazepine

Carbamazepine is an enzyme inducer and typically causes decreases in drug exposure, however, slightly increased levels of selegiline and its metabolites were seen after single application of **EMSAM** 6mg/24hours in subjects who had received carbamazepine (400mg/day) for 14 days. Changes in plasma selegiline concentrations were nearly two-fold, and variable across the subject population. The clinical relevance of these observations is unknown. Carbamazepine is contraindicated with MAOI's , including selegiline. **(**see **CONTRAINDICATIONS)**

Ibuprofen

In subjects who had received **EMSAM** 6mg/24hours for 11 days, combined administration with the CYP2C9 substrate ibuprofen (800 mg single dose) did not affect the pharmacokinetics of either selegiline or ibuprofen.

Ketoconazole

Seven-day treatment with ketoconazole (200mg/day), a potent inhibitor of CYP3A4, did not affect the steady-state pharmacokinetics of selegiline in subjects who received **EMSAM** 6mg/24hours for seven days and no differences in the pharmacokinetics of ketoconazole were observed.

Levothyroxine

In healthy subjects who had received **EMSAM** 6mg/24hours for 10 days, single dose administration with levothyroxine (150 µg) did not alter the pharmacokinetics of either selegiline or levothyroxine (as judged by T_3 and T_4 plasma levels).

Olanzapine

In subjects who had received **EMSAM** 6mg/24hours for 10 days, co-administration with olanzapine, a substrate for CYP1A2, CYP2D6, and possibly CYP2A6, did not affect the pharmacokinetics of either selegiline or olanzapine.

Phenylpropanolamine (PPA)

In subjects who had received EMSAM 6mg/24hours for 9 days, co-administration with PPA (25mg every 4 hours for 24 hours) did not affect the pharmacokinetics of PPA. There was a higher incidence of significant blood pressure elevations with the co-administration of EMSAM and PPA than with PPA alone, suggesting a possible pharmacodynamic interaction. It is prudent to avoid the concomitant use of sympathomimetic agents with EMSAM.

Pseudoephedrine

EMSAM 6mg/24hours for 10 days, co-administered with pseudoephedrine (60mg three times a day) did not affect the pharmacokinetics of pseudoephedrine. The effect of pseudoephedrine on EMSAM was not examined. There were no clinically significant changes in blood pressure during pseudoephedrine administration alone, or in combination with **EMSAM**. Nonetheless, it is prudent to avoid the concomitant use of sympathomimetic agents with **EMSAM**.

Risperidone

In subjects who had received **EMSAM** 6mg/24hours for 10 days, co-administration with risperidone (2 mg per day for 7 days), a substrate for CYP2D6, did not affect the pharmacokinetics of either selegiline or risperidone.

Tyramine

Selegiline (the drug substance of **EMSAM**) is an irreversible inhibitor of monoamine oxidase (MAO), a ubiquitous intracellular enzyme. MAO exists as two isoenzymes, referred to as MAO-A and MAO-B. Selegiline shows greater affinity for MAO-B; however, as selegiline concentration increases, this selectivity is lost with resulting dose-related inhibition of MAO-A. Intestinal MAO is predominantly type A, while in the brain both isoenzymes exist.

MAO plays a vital physiological role in terminating the biological activity of both endogenous and exogenous amines. In addition to their role in the catabolism of monoamines in the CNS, MAOs are also important in the catabolism of exogenous amines found in a variety of foods and drugs. MAO in

the gastrointestinal tract (primarily type A) provides protection from exogenous amines with vasopressor actions, such as tyramine, which if absorbed intact can cause a hypertensive crisis, the so-called "cheese reaction." If a large amount of tyramine is absorbed systemically, it is taken up by adrenergic neurons and causes norepinephrine release from neuronal storage sites with resultant elevation of blood pressure. While most foods contain negligible amounts or no tyramine, a few food products (See **WARNINGS**) may contain large amounts of tyramine that represent a potential risk for patients with significant inhibition of intestinal MAO-A resulting from administration of MAO inhibitors. Tyramine-containing nutritional supplements should be avoided by patients taking **EMSAM**.

Animal studies have indicated the transdermal administration of selegiline via **EMSAM** 6mg/24hours allows for critical levels of MAO inhibition to be achieved in the brain while avoiding levels of gastrointestinal inhibition. To further define the risk of hypertensive crises with use of **EMSAM**, several Phase I tyramine challenge studies were conducted both with and without food.

Fourteen tyramine challenge studies including 214 healthy subjects (age range 18-65; 31 subjects >50 years of age) were conducted to determine the pressor effects of oral tyramine with concurrent **EMSAM** treatment (6mg/24hours -12mg/24hours), measured as the dose of tyramine required to raise systolic blood pressure by 30mmHg (TYR30). Studies were conducted with and without concomitant administration of food. Studies conducted with food are most relevant to clinical practice since tyramine typically will be consumed in food. A high-tyramine meal is considered to contain up to 40mg of tyramine.

One study using a crossover design in 13 subjects investigated tryamine pressor doses (TYR30) after administration of **EMSAM** 6mg/24hours and oral selegiline (5mg twice daily) for 9 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 338mg and 385 in subjects treated with EMSAM and oral selegiline, respectively.

Another study using a crossover design in 10 subjects investigated tyramine pressor doses after administration of **EMSAM** 6mg/24hours or tranylcypromine 30mg/day for 10 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 270 mg in subjects treated with **EMSAM** 6mg/24hours and 10mg in subjects treated with tranylcypromine.

In a third crossover study, tyramine without food was administered to 12 subjects. The mean tyramine pressor doses (TYR30) after administration of **EMSAM** 6mg/24hours for 9 and 33 days were 292mg and 204mg, respectively. The lowest pressor dose was 50mg in one subject in the 33-day group.

Tyramine pressor doses were also studied in 11 subjects after extended treatment with EMSAM 12mg/24hours. At 30, 60, and 90 days, the mean pressor doses (TYR30) of tyramine administered without food were 95mg, 72mg, and 88mg, respectively. The lowest pressor dose without food was 25mg in 3 subjects at day 30 while on **EMSAM** 12mg/24hours. Eight subjects from this study, with a mean tyramine pressor dose of 64mg at 90 days, were subsequently administered tyramine with food, resulting in a mean pressor dose of 172mg (2.7 times the mean pressor dose observed without food, $p < 0.003$).

With the exception of one study (N = 153), the phase III clinical development program was conducted without requiring a modified diet (N= 2553, 1606 at 6mg/24hours, and 947 at 9mg/24hours or 12mg/24hours). No hypertensive crises were reported in any patient receiving **EMSAM**.

In its entirety, the data for **EMSAM** 6mg/24hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9mg/24hours and

12mg/24hours, patients receiving these doses should follow Dietary Modifications Required for Patients Taking **EMSAM** 9mg/24hours and 12mg/24hours. (See **WARNINGS**.)

Warfarin

Warfarin is a substrate for CYP2C9 and CYP3A4 metabolism pathways. In healthy volunteers titrated with Coumadin® (warfarin sodium) to clinical levels of anticoagulation (INR of 1.5 to 2), co-administration with **EMSAM** 6mg/24hours for 7 days did not affect the pharmacokinetics of the individual warfarin enantiomers. **EMSAM** did not alter the clinical pharmacodynamic effects of warfarin as measured by INR, Factor VII or Factor X levels.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Carcinogenesis

In an oral carcinogenicity study in rats, selegiline given in the diet for 104 weeks was not carcinogenic up to the highest evaluable dose tested (3.5 mg/kg/day, which is 3 times the oral maximum recommended human dose on a mg/m^2 basis).

Carcinogenicity studies have not been conducted with transdermal administration of selegiline.

Mutagenesis

Selegiline induced mutations and chromosomal damage when tested in the *in vitro* mouse lymphoma assay with and without metabolic activation. Selegiline was negative in the Ames assay, the *in vitro* mammalian chromosome aberration assay in human lymphocytes, and the *in vivo* oral mouse micronucleus assay.

Impairment of Fertility

A mating and fertility study was conducted in male and female rats at transdermal doses of 10, 30, and 75 mg/kg/day of selegiline (8, 24 and 60 times the maximum recommended human dose of EMSAM [12mg/24hours on a mg/m^2 basis). Slight decreases in sperm concentration and total sperm count were observed at the high dose; however, no significant adverse effects on fertility or reproductive performance were observed.

Teratogenic Effects - Pregnancy Category C

In an embryofetal development study in rats, dams were treated with transdermal selegiline during the period of organogenesis at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the maximum recommended human dose [MRHD] of EMSAM [12 mg/24hours] on a mg/m^2 basis). At the highest dose there was a decrease in fetal weight and slight increases in malformations, delayed ossification (also seen at the mid dose), and embryofetal post-implantation lethality. Concentrations of selegiline and its metabolites in fetal plasma were generally similar to those in maternal plasma. In an *oral* embryofetal development study in rats, a decrease in fetal weight occurred at the highest dose tested (36 mg/kg; no-effect dose 12 mg/kg); no increase in malformations was seen.

In an embryofetal development study in rabbits, dams were treated with transdermal selegiline during the period of organogenesis at doses of 2.5, 10, and 40 mg/kg/day (4, 16, and 64 times the MRHD on a mg/m^2 basis). A slight increase in visceral malformations was seen at the high dose. In an *oral*

embryofetal development study in rabbits, increases in total resorptions and post-implantation loss, and a decrease in the number of live fetuses per dam, occurred at the highest dose tested (50 mg/kg; no-effect dose 25 mg/kg).

In a prenatal and postnatal development study in rats, dams were treated with transdermal selegiline at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the MRHD on a mg/m^2 basis) on days 6-21 of gestation and days 1-21 of the lactation period. An increase in post-implantation loss was seen at the mid and high doses, and an increase in stillborn pups was seen at the high dose. Decreases in pup weight (throughout lactation and post-weaning periods) and survival (throughout lactation period), retarded pup physical development, and pup epididymal and testicular hypoplasia, were seen at the mid and high doses. Retarded neurobehavioral and sexual development was seen at all doses. Adverse effects on pup reproductive performance, as evidenced by decreases in implantations and litter size, were seen at the high dose. These findings suggest persistent effects on the offspring of treated dams. A no-effect dose was not established for developmental toxicity. In this study concentrations of selegiline and its metabolites in milk were ~ 15 and 5 times, respectively, the concentrations in plasma, indicating that the pups were directly dosed during the lactation period.

There are no adequate and well-controlled studies in pregnant women. EMSAM should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of EMSAM on labor and delivery in humans is unknown.

Nursing Mothers

In a prenatal and postnatal study of transdermal selegiline in rats, selegiline and metabolites were excreted into the milk of lactating rats. The levels of selegiline and metabolites in milk were approximately 15 and 5 times, respectively, steady state levels of selegiline and metabolites in maternal plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised administering **EMSAM** to a nursing mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (See BOX **WARNING** and **WARNINGS**- Clinical Worsening and Suicide Risk).

Anyone considering the use of **EMSAM** in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

One hundred ninety-eight (198) elderly (≥ 65 years of age) patients participated in clinical studies with **EMSAM** 6mg/24hours to 12mg/24hours. There were no overall differences in effectiveness between elderly and younger patients. In short-term, placebo-controlled depression trials, patients age 50 and older appeared to be at higher risk for rash (4.4% **EMSAM** versus 0% placebo) than younger patients (3.4% **EMSAM** versus 2.4% placebo).

ADVERSE EVENTS

The premarketing development program for **EMSAM** included selegiline exposures in patients and/or normal subjects from two different groups of studies: 702 healthy subjects in clinical pharmacology/pharmacokinetics studies and 2,036 exposures from patients in controlled and uncontrolled major depressive disorder clinical trials. The conditions and duration of treatment with **EMSAM** varied and included double-blind, open-label, fixed-dose, and dose titration studies of short-term and longer-term exposures. Safety was assessed by monitoring adverse events, physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term Placebo-Controlled Trials

Adverse Events Associated with Discontinuation of Treatment

Among 817 depressed patients who received **EMSAM** at doses of either 3mg/24hours (151 patients), 6mg/24hours (550 patients) or 6mg/24hours, 9mg/24hours, and 12mg/24hours (116 patients) in placebo-controlled trials of up to 8 weeks in duration, 7.1% discontinued treatment due to an adverse event as compared with 3.6% of 668 patients receiving placebo. The only adverse event associated with discontinuation, in at least 1% of EMSAM -treated patients at a rate at least twice that of placebo, was application site reaction (2% EMSAM vs. 0% placebo).

Adverse Events Occurring at an Incidence of 2% or More Among **EMSAM**-Treated Patients

Table 1 enumerates adverse events that occurred at an incidence of 2% or more (rounded to the nearest percent) among 817 depressed patients who received **EMSAM** in doses ranging from 3 to 12mg/24hours in placebo-controlled trials of up to 8 weeks in duration. Events included are those occurring in 2% or more of patients treated with **EMSAM** and for which the incidence in patients treated with **EMSAM** was greater than the incidence in placebo-treated patients.

Only one adverse event was associated with a reporting of at least 5% in the EMSAM group, and a rate at least twice that in the placebo group, in the pool of short-term, placebo-controlled studies: application site reactions (see Application Site Reactions, below). In one such study which utilized higher mean doses of EMSAM than that in the entire study pool, the following events met these criteria: application site reactions, insomnia, diarrhea, and pharyngitis.

These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physicians with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

TABLE 1
Treatment-Emergent Adverse Events:
Incidence in Placebo-Controlled Clinical Trials for
Major Depressive Disorder With EMSAM[(1)]

Body System/Preferred Term	EMSAM (N=817)	Placebo (N=668)
	(% of Patients Reporting Event)	
Body as a Whole		
Headache	18	17
Digestive		
Diarrhea	9	7
Dyspepsia	4	3
Nervous		
Insomnia	12	7
Dry Mouth	8	6
Respiratory		
Pharyngitis	3	2
Sinusitis	3	1
Skin		
Application Site Reaction	24	12
Rash	4	2

(1) Events reported by at least 2% of patients treated with **EMSAM** are included, except the following events which had an incidence on placebo treatment ≥ to **EMSAM**: infection, nausea, dizziness, pain, abdominal pain, nervousness, back pain, asthenia, anxiety, flu syndrome, accidental injury, somnolence, rhinitis, and palpitations.

Application Site Reactions

In the pool of short-term, placebo-controlled major depressive disorder studies, application site reactions (ASR's) were reported in 24% of EMSAM-treated patients and 12% of placebo-treated patients. Most ASR's were mild or moderate in severity. None were considered serious. ASR's led to dropout in 2% of EMSAM-treated patients and no placebo-treated patients.

In one such study which utilized higher mean doses of EMSAM, ASR's were reported in 40% of EMSAM-treated patients and 20% of placebo-treated patients. Most of the ASR's in this study were described as erythema and most resolved spontaneously, requiring no treatment. When treatment was administered, it most commonly consisted of dermatological preparations of corticosteroids.

Male and Female Sexual Dysfunction with MAO Inhibitors

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 2 shows

that the incidence rates of sexual side effects in patients with major depressive disorder are comparable to the placebo rates in placebo-controlled trials.

TABLE 2. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials With EMSAM

Adverse Event	EMSAM	Placebo
	IN MALES ONLY	
	(N=304)	(N=256)
Abnormal Ejaculation	1.0%	0.0%
Decreased Libido	0.7%	0.0%
Impotence	0.7%	0.4%
Anorgasmia	0.2%	0.0%
	IN FEMALES ONLY	
	(N=513)	(N=412)
Decreased Libido	0.0%	0.2%

There are no adequately designed studies examining sexual dysfunction with EMSAM treatment.

Vital Sign Changes

EMSAM and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. In the pool of short-term, placebo-controlled major depressive disorder studies, 3.0% of **EMSAM**-treated patients and 1.5% of placebo-treated patients experienced a low systolic blood pressure, defined as a reading less than or equal to 90mmHg with a change from baseline of at least 20mmHg. In one study which utilized higher mean doses of **EMSAM**, 6.2% of **EMSAM**-treated patients and no placebo-treated patients experienced a low standing systolic blood pressure by these criteria.

In the pool of short-term major depressive disorder trials, 9.8% of **EMSAM**-treated patients and 6.7% of placebo-treated patients experienced a notable orthostatic change in blood pressure, defined as a decrease of at least 10mmHg in mean blood pressure with postural change.

Weight Changes

In placebo-controlled studies (6-8 weeks), the incidence of patients who experienced ≥5% weight gain or weight loss is shown in Table 3.

TABLE 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials With EMSAM

Weight Change	EMSAM	Placebo
	(N=757)	(N=614)
Gained ≥ 5%	2.1%	2.4%
Lost ≥ 5%	5.0%	2.8%

In these trials, the mean change in body weight among **EMSAM**-treated patients was -1.2 lbs compared to +0.3 lbs in placebo-treated patients.

Laboratory Changes

EMSAM and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with **EMSAM**.

ECG Changes

Electrocardiograms (ECGs) from **EMSAM** (N=817) and placebo (N=668) groups in controlled studies were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for clinically significant changes from baseline in these variables.

No clinically meaningful changes in ECG parameters from baseline to final visit were observed for patients in controlled studies.

Other Events Observed During the Premarketing Evaluation of EMSAM

During the premarketing assessment in major depressive disorder, **EMSAM** was administered to 2036 patients in phase III studies. The conditions and duration of exposure to **EMSAM** varied and included double-blind and open-label studies.

In the tabulations that follow, reported adverse events were classified using a standard COSTART–based dictionary terminology. All reported adverse events are included except those already listed in Table 1 or elsewhere in labeling, and those events occurring in only one patient. It is important to emphasize that although the events occurred during treatment with **EMSAM,** they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: *Frequent*: Chest pain, neck pain. *Infrequent:* Bacterial infection, fever, cyst, fungal infection, chills, viral infection, suicide attempt, neck rigidity, pelvic pain, photosensitivity reaction, face edema, flank pain, hernia, intentional injury, neoplasm, generalized edema, overdose. *Rare:* Body odor, halitosis, heat stroke, parasitic infection, malaise, moniliasis.

Cardiovascular System: *Frequent:* Hypertension. *Infrequent:* Vasodilatation, tachycardia, migraine, syncope, atrial fibrillation, peripheral vascular disorder. *Rare:* Myocardial infarct.

Digestive System: *Frequent:* Constipation, flatulence, anorexia, gastroenteritis, vomiting. *Infrequent:* Increased appetite, thirst, periodontal abscess, eructation, gastritis, colitis, dysphagia, tongue edema, glossitis, increased salivation, abnormal liver function tests, melena, tongue disorder, tooth caries. *Rare:* GI neoplasia, rectal hemorrhage.

Hemic and Lymphatic System *Frequent:* Ecchymosis. *Infrequent*: Anemia, lymphadenopathy. *Rare:* Leukocytosis, leukopenia, petechia.

Metabolic and Nutritional: *Frequent***:** Peripheral edema. *Infrequent*: Hyperglycemia, increased SGPT, edema, hypercholesteremia, increased SGOT, dehydration, alcohol intolerance, hyponatremia, increased lactic dehydrogenase. *Rare:* Increased alkaline phosphatase, bilirubinemia, hypoglycemic reaction.

Musculoskeletal System: *Frequent*: Myalgia, pathological fracture. *Infrequent*: Arthralgia, generalized spasm, arthritis, myasthenia, arthrosis, tenosynovitis. *Rare:* Osteoporosis.

Nervous System: *Frequent***:** Agitation, paresthesia, thinking abnormal, amnesia. *Infrequent*: Leg cramps, tremor, vertigo, hypertonia, twitching, emotional lability, confusion, manic reaction, depersonalization, hyperkinesias, hostility, myoclonus, circumoral paresthesia, hyperesthesia, increased libido, euphoria, neurosis, paranoid reaction; *Rare:* Ataxia.

Respiratory System: *Frequent***:** Cough increased, bronchitis. *Infrequent*: Dyspnea, asthma, pneumonia, laryngismus; *Rare:* Epistaxis, laryngitis, yawn.

Skin and Appendages: *Frequent*: Pruritus, sweating, acne. *Infrequent*: Dry skin, maculopapular rash, contact dermatitis, urticaria, herpes simplex, alopecia, vesiculobullous rash, herpes zoster, skin hypertrophy, fungal dermatitis, skin benign neoplasm; *Rare:* Eczema.

Special Senses: *Frequent*: Taste perversion, tinnitus. *Infrequent*: Dry eyes, conjunctivitis, ear pain, eye pain, otitis media, parosmia; *Rare:* Mydriasis, otitis external, visual field defect.

Urogenital System: *Frequent:* Urinary tract infection, urinary frequency, dysmenorrhea, metrorrhagia. *Infrequent*: Urinary tract infection (male), vaginitis, cystitis (female), hematuria (female), unintended pregnancy, dysuria (female), urinary urgency (male and female), vaginal moniliasis, menorrhagia, urination impaired (male), breast neoplasm (female), kidney calculus (female), vaginal hemorrhage, amenorrhea, breast pain, polyuria (female).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

EMSAM is not a controlled substance.

Physical and Psychological Dependence

Several animal studies have assessed potential for abuse and/or dependence with chronic selegiline administration. None of these studies demonstrated a potential for selegiline abuse or dependence.

EMSAM has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of EMSAM misuse or abuse (e.g., development of tolerance, increases in dose, or drug-seeking behavior).

OVERDOSAGE

There are no specific antidotes for **EMSAM**. If symptoms of overdosage occur, immediately remove the **EMSAM** system and institute appropriate supportive therapy. For contemporary consultation on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222.

EMSAM is considered to be an irreversible, MAOI at therapeutic doses and, in overdosage, is likely to cause excessive MAO-A inhibition, and may result in the signs and symptoms resembling overdosage with other non-selective, oral MAOI antidepressants (e.g., tranylcypromine (Parnate®), phenelzine (Nardil®), or isocarboxazide (Marplan®).

Overdosage with Non-Selective MAO Inhibition:

NOTE: The following is provided for reference only; it does not describe events that have actually been observed with selegiline in overdosage. No information regarding overdose by ingestion of **EMSAM** is available.

Typical signs and symptoms associated with overdosage of non-selective MAOI antidepressants may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur, and peak effects may not be observed for 24-48 hours. Since death has been reported following overdosage with MAOI agents, hospitalization with close monitoring during this period is essential.

Overdosage with MAOI agents is typically associated with CNS and cardiovascular toxicity. Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, convulsions, coma, rapid and irregular pulse, hypertension, hypotension and vascular collapse, precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin. Type and intensity of symptoms may be related to extent of the overdosage.

Treatment should include supportive measures, with pharmacological intervention as appropriate. Symptoms may persist after drug washout because of the irreversible inhibitory effects of these agents on systemic MAO activity. With overdosage, in order to avoid the occurrence of hypertensive crisis ("cheese reaction"), dietary tyramine should be restricted for several weeks beyond recovery to permit regeneration of the peripheral MAO-A isoenzyme.

DOSAGE AND ADMINISTRATION

Initial Treatment

EMSAM should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm once every 24 hours. The recommended starting dose and target dose for **EMSAM** is 6mg/24hours. **EMSAM** has been systematically evaluated and shown to be effective in a dose range of 6mg/24hours to 12mg/24hours. However the trials were not designed to assess if higher doses are more effective than the lowest effective dose of 6mg/24hours. Based on

clinical judgment, if dose increases are indicated for individual patients, they should occur in dose increments of 3mg/24hours (up to a maximum dose of 12mg/24hours) at intervals of no less than two weeks. As with all antidepressant drugs, full antidepressant effect may be delayed.

Patients should be informed that tyramine-rich foods and beverages should be avoided beginning on the first day of EMSAM 9mg/24hours or 12mg/24hours treatment and should continue to be avoided for two weeks after a dose reduction to EMSAM 6mg/24hours or following the discontinuation of EMSAM 9mg/24hours or 12mg/24hours (See **WARNINGS**).

Special Populations

No dosage adjustment is required for patients with mild to moderate renal or hepatic impairment. The recommended dose for elderly patients (≥ 65 years) is **EMSAM** 6mg/24hours daily. Dose increases, in the elderly, should be made with caution and patients should be closely observed for postural changes in blood pressure throughout treatment.

How to Use EMSAM

1. EMSAM should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm. A new application site should be selected with each new patch to avoid re-application to the same site on consecutive days. Patches should be applied at approximately the same time each day.

2. Apply the patch to an area of skin that is not hairy, oily, irritated, broken, scarred or calloused. Do not place the patch where your clothing is tight which could cause the patch to rub off.

3. After you have selected the site for your patch, wash the area gently and thoroughly with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.

4. Just before you apply the patch, remove it from the pouch. Remove half of the protective backing and throw it away. Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers.

5. Press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface.

6. After you have applied the patch, wash your hands thoroughly with soap and water to remove any medicine that may have gotten on them. Do not touch your eyes until after you have washed your hands.

7. After 24 hours, remove the patch. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.

8. Throw away the folded patch so that children and/or pets cannot reach it.

9. Wash your hands with soap and water.

10. If your patch falls off, apply a new patch to a new site and resume your previous schedule.

11. Only one EMSAM patch should be worn at a time.

12. Avoid exposing the EMSAM application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Maintenance Treatment

It is generally agreed that episodes of depression require several months or longer of sustained pharmacologic therapy. The benefit of maintaining depressed patients on therapy with **EMSAM** at a dose of 6mg/24hours after achieving a responder status for an average duration of about 25 days was demonstrated in a controlled trial (see **CLINICAL EFFICACY TRIALS** and **INDICATIONS AND USAGE**). The physician who elects to use **EMSAM** for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

HOW SUPPLIED

EMSAM is supplied as 6mg/24 hours (20mg/20cm^2), 9mg/24 hours (30mg/30cm^2)and 12mg/24 hours (40mg/40cm^2) transdermal systems.

They are available as:
NDC 39506-033-30 6mg/24hours (20mg/20cm^2) box of 30 transdermal systems.
NDC 39506-044-30 9mg/24 hours (30mg/30cm^2)box of 30 transdermal systems.
NDC 39506-055-30 12mg/24 hours (40mg/40cm^2) box of 30 transdermal systems.

STORAGE AND DISPOSAL

Store at 20º to 25º C (68º to 77º F) [see USP Controlled Room Temperature]. Do not store outside of the sealed pouch. Apply immediately upon removal from the protective pouch. Discard used **EMSAM** in household trash in a manner that prevents accidental application or ingestion by children, pets or others.

DISTRIBUTED BY:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

MANUFACTURED FOR:
Somerset Pharmaceuticals, Inc.
Tampa, FL 33607 USA

Rx Only

Tampa, FL 33607
Literature issued XXXXXX XXXX
EMSAM:R0.2
Revised Proposed Labeling- 2/24/06

MEDICATION GUIDE

EMSAM® [EM sam]

Generic Name: selegiline transdermal system

Rx only

Read this Medication Guide carefully before you start using **EMSAM** and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about **EMSAM**, ask your doctor or pharmacist.

IMPORTANT: Be sure to read the section of this Medication Guide beginning with "What is the most important information I should know about EMSAM?" It contains important information about certain changes in diet that might be needed, other medications to avoid, and other important information about this medication. It immediately follows the next section called "About Using Antidepressants in Children and Teenagers."

ABOUT USING ANTIDEPRESSANTS IN CHILDREN AND TEENAGERS

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:
1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves.

Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called *suicidality* or *being suicidal*.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. ***No one committed suicide in these studies***, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with
- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her healthcare provider:
• Once a week for the first 4 weeks
• Every 2 weeks for the next 4 weeks
• After taking the antidepressant for 12 weeks
• After 12 weeks, follow your healthcare provider's advice about how often to come back
• More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

3. You Should Watch for Certain Signs If Your Child is Taking an Antidepressant

Contact your child's healthcare provider ***right away*** if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:
• Thoughts about suicide or dying
• Attempts to commit suicide
• New or worse depression
• New or worse anxiety
• Feeling very agitated or restless
• Panic attacks
• Difficulty sleeping (insomnia)
• New or worse irritability
• Acting aggressive, being angry, or violent
• Acting on dangerous impulses
• An extreme increase in activity and talking
• Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, the FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine (Luvox®), and clomipramine (Anafranil®).

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?
No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants.

Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

What is the most important information I should know about EMSAM?

1. **EMSAM contains a medicine called a monoamine oxidase inhibitor, also called a MAOI. MAOI medicines, including EMSAM can cause a sudden, large increase in blood pressure (hypertensive crisis) if you eat foods and drinks that contain high amounts of tyramine. A hypertensive crisis can be a life-threatening condition.** See "What are the possible side effects of EMSAM?" for signs and symptoms of a hypertensive crisis.

- **EMSAM comes in three different doses and patch sizes:**
  - a 6mg/24hours patch
  - a 9mg/24hours patch
  - a 12mg/24hours patch

- **You must avoid (not eat or drink) certain foods and drinks while using EMSAM 9mg/24hours and EMSAM 12mg/24hours patches and for 2 weeks after stopping EMSAM 9mg/24hours and EMSAM 12mg/24hours patches.** (The table below lists these foods and drinks)**. The table also lists foods and drinks that are okay to eat and drink while using EMSAM 9mg/24hours and EMSAM 12mg/24hours patches.**

- **You do not have to make any diet changes with the EMSAM 6mg/24hours patch.**

Type of Food and Drink	*Tyramine-Rich Foods and Drinks to Avoid*	**Acceptable Foods and Drinks, Containing No or Little Tyramine**
Meat, Poultry and Fish	• **Air dried, aged and fermented meats, sausages and salamis** • **pickled herring** • **and any spoiled or improperly stored meat, poultry and fish. These are foods that have a change in color, odor, or become moldy.**	• **Fresh meat, poultry and fish, including fresh processed meats (such as lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)**

	• spoiled or improperly stored animal livers.	
Vegetables	• **Broad bean pods (fava bean pods)**	• **All other vegetables**
Dairy (milk products)	• **Aged cheeses**	• **Processed cheeses, mozzarella, ricotta cheese, cottage cheese, and yogurt**
Drinks	• **All tap beers, and other beers that have not been pasteurized**	• As with other antidepressants, concomitant use of alcohol with **EMSAM** is not recommended. (Bottled and canned beers and wines contain little or no tyramine)
Other	• **Concentrated yeast extract (such as Marmite)** • **Sauerkraut** • **Most soybean products (including soy sauce and tofu)** • **over-the-counter supplements containing tyramine**	• **Brewer's yeast, bakers yeast** • **Soy milk** • **Pizzas from commercial chain-restaurants prepared with cheeses low in tyramine.**

[1] Adapted from K. I. Shulman, S. E. Walker, Psychiatric Annals 2001; 31:378-384

- All foods you eat must be fresh or properly frozen.
- Avoid foods when you do not know their storage conditions.

2. EMSAM can cause serious and potentially life-threatening reactions if used with certain other medicines. Do not take the following medicines while using EMSAM, and for 2 weeks after stopping EMSAM:

- other medicines to treat depression (antidepressants) including other MAOI medicines
- medicine which contains selegiline (such as Eldepryl®).
- St. John's Wort (a herbal supplement)
- Demerol® (meperidine), or medicines that contain meperidine (a narcotic pain medicine) or the pain medicines tramadol, methadone, or propxyphene
- Tegretol (carbamazepine), or other medicines that contain carbamazepine (a seizure medicine)
- Trileptal (oxcarbazepine), or other medicines that contain oxcarbazepine (a seizure medicine)
- Cold or cough preparations that contain dextromethorphan.
- Flexeril or other medicines that contain cyclobenzaprine (a medicine used to treat muscle spasms)
- decongestant medicines, found in many products to treat cold symptoms
- over-the-counter diet pills or herbal weight-loss products
- any herbal or dietary supplement that contains tyramine
- medicines called amphetamines, also called stimulants or "uppers"
- BuSpar® (buspirone HCL), an anxiety medicine

Some of these medicines will have to be stopped for at least a week before you can start using EMSAM.

What is EMSAM?

EMSAM is a skin patch (transdermal system) used to treat major depression. The skin patch delivers the medicine through your skin and into your bloodstream.

EMSAM has not been studied for the treatment of depression in children under 18 years of age.

Who should not use EMSAM?

Do not use EMSAM if you are:

- **taking certain other medicines.** See "What is the most important information I should know about EMSAM?"
- **allergic to anything in EMSAM.** See the end of this Medication Guide for a complete list of ingredients in EMSAM.

What should I tell my doctor before starting EMSAM?

Tell your doctor about all your medical conditions, including if you:

- **have any heart problems**
- **have or had manic episodes** (a mental condition that causes "high" moods).
- **have or had seizures** (convulsions or "fits").
- **tend to get dizzy or faint**
- **are pregnant or planning to become pregnant.** It is not known if **EMSAM** can harm your unborn baby.
- **are breastfeeding.** It is not known if **EMSAM** passes into your milk or if it can harm your baby.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. **EMSAM can cause a serious and life-threatening reaction if used with certain other medicines.** See ''What is the most important information I should know about EMSAM?''

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist. Do not take any new medicine while using EMSAM, and for 2 weeks after you stop using it, before talking with your doctor.

How should I use EMSAM?

See the end of this Medication Guide for "How to Use and Apply an EMSAM Patch".

- Use **EMSAM** exactly as prescribed by your doctor. **Use only one patch at a time.** Change the patch once a day (every 24 hours). Choose a time of day that works best for you.

- Your doctor will prescribe a dose of **EMSAM** based on your condition. Your doctor may change your dose if needed.

- Talk to your doctor often about your condition. You may notice an improvement in your condition with **EMSAM** therapy after several weeks. **Do not stop or change your treatment with EMSAM without talking to your doctor.**

- **Make sure you do not eat foods or drink beverages that contain high amounts of tyramine while using EMSAM 9mg/24hours or EMSAM 12mg/24hours patches, and for 2 weeks after you stop using them.**

- If you use more than one **EMSAM patch at a time**, remove **EMSAM patches** right away and call your doctor or local Poison Control Center.

- Avoid exposing the EMSAM application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

- Tell your doctor if you plan to have surgery. Also, tell your surgeon that you take EMSAM. EMSAM should be stopped 10 days before you have elective surgery.

What should I avoid while using EMSAM?

- **You must not eat foods or drink beverages foods and drinks that contain high amounts of tyramine while using EMSAM 9mg/24hours and 12mg/24hours patches.** You do not have to make any diet changes with the EMSAM 6 mg/24hours patch.. See "What is the most important information I should know about EMSAM?"

- **Do not take other medicines while using EMSAM or for 2 weeks after you stop using it unless your doctor has told you it is okay.** See "What is the most important information I should know about EMSAM?"

- **Do not drive or operate dangerous machinery until you know how EMSAM affects you. EMSAM may reduce your judgment, ability to think, or coordination.**

- **Drinking alcoholic beverages is not recommended while using EMSAM.**

What are the possible side effects of EMSAM?

EMSAM:

- **can cause a sudden, large increase in blood pressure, (''hypertensive crisis'') if you eat certain foods and drinks during treatment. See** "What is the most important Information I should know about EMSAM?" **A hypertensive crisis can lead to stroke and death.** Symptoms of a hypertensive crisis include the sudden onset of severe headache, nausea, stiff neck, a fast heartbeat or a change in the way your heart beats (palpitations), a lot of sweating, and confusion. **If you suddenly have these symptoms, get medical care right away.**

- **can cause serious and potentially life-threatening reactions if used with certain other medicines.** See "What is the most important Information I should know about EMSAM?"

- **may worsen your depression, give you suicidal thoughts, or cause unusual changes in behavior.** Call your doctor right away if you feel worse with EMSAM.

- **may cause a mental condition called mania or hypomania** (mental condition which causes high moods) in people who have a history of mania.

- **can cause low blood pressure.** Lie down if you feel dizzy, faint, or lightheaded. Change your position slowly if low blood pressure is a problem for you. Tell your doctor if you have these symptoms. You may need a lower dose of **EMSAM**.

The most common side effect of **EMSAM** is a skin reaction where the patch is placed.
You may see mild redness at the site when a patch is removed. This redness should go away within several hours after removing the patch. If irritation or itching continues, tell your doctor.

These are not all the side effects of **EMSAM**. For more information, ask your doctor or pharmacist.

How do I store EMSAM?

- Store **EMSAM** at 68° to 77°F (20° to 25°C).
- Store **EMSAM** in its sealed pouch until use.
- **Keep EMSAM and all medicines out of the reach of children and away from pets.**

General information about EMSAM

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not give **EMSAM** to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about **EMSAM**. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about **EMSAM** that is written for health professionals.

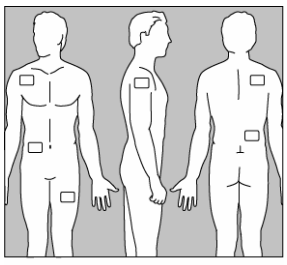
For more information, call 1-800-321-1335 or visit www.EMSAM.com

What are the ingredients in EMSAM?
Active Ingredient: Selegiline
Inactive Ingredients: acrylic adhesive, ethylene vinyl acetate, low density polyethylene, polyester, polyurethane, and silicon coated polyethylene terephthalate

How to Use and Apply an EMSAM Patch

Read these instructions carefully before you apply EMSAM. Ask your doctor or pharmacist about anything you do not understand.

- Apply a new **EMSAM** patch every day (24hours).
- **Wear only one EMSAM patch at a time.** Wear one EMSAM patch all the time until it is time to apply a new one.
- Remove a used patch before applying a new one.
- Change the patch at the same time each day.
- Apply an EMSAM patch to dry, smooth skin on your upper chest or back (below the neck and above the waist), upper thigh or to the outer surface of the upper arm. Choose a new site each time you change your patch. Do not use the same site two days in a row. (See picture 1 for skin sites that may be used.)



Picture 1. Skin sites for EMSAM patch (Do not use more than one patch at a time)

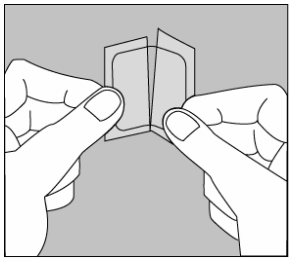
- Apply an EMSAM patch to an area of skin that is not hairy, oily, irritated, broken, scarred or calloused. Do not place the patch where your clothing is tight, which could cause the patch to rub

off.

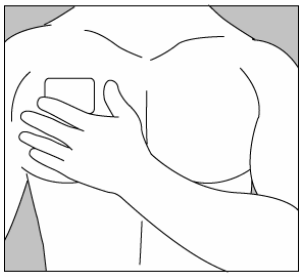
- After you have selected the site for your patch, wash the area gently and well with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.

- Just before you apply the patch, remove it from its sealed pouch. **Do not keep or store the patch outside of the sealed pouch. Never cut an EMSAM patch into smaller pieces to use.**

- Remove half of the protective backing and throw it away. (See picture 2) Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers. With your fingertips, press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface. (See picture 3.)



Picture 2. Removing the protective backing from an EMSAM patch.



Picture 3. Applying an EMSAM patch

After you have applied the patch, wash your hands well with soap and water to remove any medicine that may have gotten on them. **Do not touch your eyes until after you have washed your hands.**

- After 24 hours, remove the patch slowly and carefully to avoid damaging the skin. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.

- Throw away the folded patch so that children and pets cannot reach it. This patch still contains some medicine and could harm a child or pet.

- Gently wash the old application site with warm water and a mild soap to remove any sticky material (adhesive) that stays on your skin after removing the patch. A small amount of baby oil may also be used to remove any adhesive. You may need to use a medical adhesive removal pad that you can get from your pharmacist. Alcohol or other dissolving liquids such as nail polish remover may cause skin irritation and should not be used.

- Wash your hands with soap and water.

- If the patch becomes loose, press it back in place. If your EMSAM patch falls off, apply a new EMSAM patch to a new site and resume your normal schedule for changing patches.

- If you forget to change your patch after 24 hours, remove the old patch, put on a new patch in a different area and continue to follow your original schedule.

This Medication Guide has been approved by the US Food and Drug Administration.

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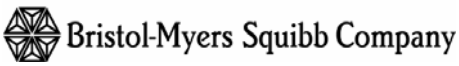

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/s/

Thomas Laughren
2/27/2006 04:02:39 PM