PDR®

61 EDITION

2007

PHYSICIANS' DESK REFERENCE®

www.PDR.net

Web | PDA | Print

PDR®

61 EDITION

2007

PHYSICIANS' DESK REFERENCE®

Executive Vice President, PDR: Kevin D. Sanborn
Senior Vice President, PDR Sales: Roseanne McCauley
Vice President, Marketing: William T. Hicks
Vice President, Regulatory Affairs: Mukesh Mehta, RPh
Vice President, PDR Services: Brian Holland
Senior Director, Pharmaceutical Solutions Sales: Anthony Sorce
PDR Sales Managers: Frank Karkowsky, Elaine Musco, Marion Reid, RPh
National Solutions Manager: Richard Zwickel
Senior Solutions Managers: Debra Goldman, Warner Stuart, Suzanne E. Yarrow, RN
Solutions Managers: Joseph Gross, Marjorie A. Jaxel, Lois Smith, Krista Turpin
Sales Coordinators: Dawn McPartland, Janet Wallendal

Director of Trade Sales: Bill Gaffney
Senior Manager, Direct Marketing: Amy Cheong

Senior Director of Product Management, Electronic Solutions: Valerie E. Berger
Director of Product Management, Monographs: Jeffrey D. Schaefer
Senior Marketing Manager: Kim Marich

Senior Director, Client Services: Stephanie Struble
Director of Operations: Robert Klein
Director of Finance: Mark S. Ritchin

Director, Editorial Services: Bette LaGow
Manager, Professional Services: Michael DeLuca, PharmD, MBA
Drug Information Specialists: Majid Kerolous, PharmD; Nermin Shenouda, PharmD; Greg Tallis, RPh
Project Editor: Lori Murray
Manager, Client Services: Travis Northern
Customer Service Supervisor: Todd Taccetta

Manager, Production Purchasing: Thomas Westburgh
PDR Production Manager: Steven Maher
PDR Index Supervisor: Shannon R. Spare
Index Editor: Allison O'Hare
Senior Production Coordinators: Gianna Caradonna, Yasmin Hernández
Production Coordinator: Nick W. Clark
Traffic Assistant: Kim Condon

Production Design Supervisor: Adeline Rich
Senior Electronic Publishing Designer: Livio Udina
Electronic Publishing Designers: Deana DiVizio, Carrie Faeth, Monika Popowitz
Production Associate: Joan K. Akerlind
Digital Imaging Manager: Christopher Husted
Digital Imaging Coordinator: Michael Labruyere

Officers of Thomson Healthcare, Inc.: *President and Chief Executive Officer:* Bob Cullen; *Chief Financial Officer:* Paul Hilger; *Chief Medical Officer:* Rich Klasco, MD, FACEP; *Executive Vice President, Medstat:* Carol Diephuis; *Executive Vice President, Micromedex:* Jeff Reihl; *Executive Vice President, PDR:* Kevin D. Sanborn; *Senior Vice President, Technology:* Michael Karaman; *Vice President, Finance:* Joseph Scarfone; *Vice President, Human Resources:* Pamela M. Bilash; *Vice President, Planning and Business Development:* Ray Zoeller; *Vice President, Product Strategy:* Anita Brown; *Vice President, Strategic Initiatives:* Timothy Murray

TABLE 3: Relationship Between INR and PT Ratios For Thromboplastins With Different ISI Values (Sensitivities)

	PT RATIOS				
	ISI 1.0	ISI 1.4	ISI 1.8	ISI 2.3	ISI 2.8
INR = 2.0-3.0	2.0-3.0	1.6-2.2	1.5-1.8	1.4-1.6	1.3-1.5
INR = 2.5-3.5	2.5-3.5	1.9-2.4	1.7-2.0	1.5-1.7	1.4-1.6

	100's	1000's	Hospital Unit-Dose Blister Package of 100
1 mg pink	NDC 0056-0169-70	NDC 0056-0169-90	NDC 0056-0169-75
2 mg lavender	NDC 0056-0170-70	NDC 0056-0170-90	NDC 0056-0170-75
2-1/2 mg green	NDC 0056-0176-70	NDC 0056-0176-90	NDC 0056-0176-75
3 mg tan	NDC 0056-0188-70	NDC 0056-0188-90	NDC 0056-0188-75
4 mg blue	NDC 0056-0168-70	NDC 0056-0168-90	
5 mg peach	NDC 0056-0172-70	NDC 0056-0172-90	NDC 0056-0172-75
6 mg teal	NDC 0056-0189-70	NDC 0056-0189-90	NDC 0056-0189-75
7-1/2 mg yellow	NDC 0056-0173-70		
10 mg white (Dye Free)	NDC 0056-0174-70		

ranges of 1.5 to 2.5 times control mean normal PT, used sensitive human brain thromboplastin. When using the less sensitive rabbit brain thromboplastins commonly employed in PT assays today, adjustments must be made to the targeted PT range that reflect this decrease in sensitivity.

The INR can be calculated as: INR = (observed PT ratio)^{ISI} where the ISI (International Sensitivity Index) is the correction factor in the equation that relates the PT ratio of the local reagent to the reference preparation and is a measure of the sensitivity of a given thromboplastin to reduction of vitamin K-dependent coagulation factors; the lower the ISI, the more "sensitive" the reagent and the closer the derived INR will be to the observed PT ratio.[1]

The proceedings and recommendations of the 1992 National Conference on Antithrombotic Therapy[2-4] review and evaluate issues related to oral anticoagulant therapy and the sensitivity of thromboplastin reagents and provide additional guidelines for defining the appropriate therapeutic regimen.

The conversion of the INR to PT ratios for the less-intense (INR 2.0-3.0) and more intense (INR 2.5-3.5) therapeutic range recommended by the ACCP for thromboplastins over a range of ISI values is shown in Table 3.[5]

[See table 3 above]

TREATMENT DURING DENTISTRY AND SURGERY The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. PT/INR determination is recommended just prior to any dental or surgical procedure. In patients undergoing minimal invasive procedures who must be anticoagulated prior to, during, or immediately following these procedures, adjusting the dosage of COUMADIN (Warfarin Sodium) to maintain the PT/INR at the low end of the therapeutic range may safely allow for continued anticoagulation. The operative site should be sufficiently limited and accessible to permit the effective use of local procedures for hemostasis. Under these conditions, dental and minor surgical procedures may be performed without undue risk of hemorrhage. Some dental or surgical procedures may necessitate the interruption of COUMADIN therapy. When discontinuing COUMADIN even for a short period of time, the benefits and risks should be strongly considered.

CONVERSION FROM HEPARIN THERAPY Since the anticoagulant effect of COUMADIN is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to COUMADIN may begin concomitantly with heparin therapy or may be delayed 3 to 6 days. To ensure continuous anticoagulation, it is advisable to continue full dose heparin therapy and that COUMADIN therapy be overlapped with heparin for 4 to 5 days, until COUMADIN has produced the desired therapeutic response as determined by PT/INR. When COUMADIN has produced the desired PT/INR or prothrombin activity, heparin may be discontinued.

COUMADIN may increase the aPTT test, even in the absence of heparin. During initial therapy with COUMADIN, the interference with heparin anticoagulation is of minimal clinical significance.

As heparin may affect the PT/INR, patients receiving both heparin and COUMADIN should have blood for PT/INR determination drawn at least:

- 5 hours after the last IV bolus dose of heparin, or
- 4 hours after cessation of a continuous IV infusion of heparin, or
- 24 hours after the last subcutaneous heparin injection.

HOW SUPPLIED

Tablets: For oral use, single scored with one face imprinted numerically with 1, 2, 2-1/2, 3, 4, 5, 6, 7-1/2 or 10 superimposed and inscribed with "COUMADIN (Warfarin Sodium)" and with the opposite face plain. COUMADIN is available in bottles and Hospital Unit-Dose Blister Packages with potencies and colors as follows:

[See second table above]

Protect from light. Store at controlled room temperature (59°-86°F, 15°-30°C). Dispense in a tight, light-resistant container as defined in the USP.

Hospital Unit-Dose Blister Packages are to be stored in carton until contents have been used.

Injection: Available for intravenous use only. Not recommended for intramuscular administration. Reconstitute with 2.7 mL of sterile Water for Injection to yield 2 mg/mL. Net contents 5.4 mg lyophilized powder. Maximum yield 2.5 mL.

5 mg vial (box of 6) NDC 0590-0324-35

Protect from light. Keep vial in box until used. Store at controlled room temperature (59°-86°F, 15°-30°C).

After reconstitution, store at controlled room temperature (59°-86°F, 15°-30°C) and use within 4 hours. Do not refrigerate. Discard any unused solution.

REFERENCES

1. Poller, L.: Laboratory Control of Anticoagulant Therapy. Seminars in Thrombosis and Hemostasis, Vol. 12, No. 1, pp. 13-19, 1986.
2. Hirsh, J.: Is the Dose of Warfarin Prescribed by American Physicians Unnecessarily High? *Arch Int Med*, Vol. 147, pp. 769-771, 1987.
3. Cook, D.J., Guyatt, H.G., Laupacis, A., Sackett, D.L.: Rules of Evidence and Clinical Recommendations on the Use of Antithrombotic Agents. Chest ACCP Consensus Conference on Antithrombotic Therapy. *Chest*, Vol. 102(Suppl), pp. 305S-311S, 1992.
4. Hirsh, J., Dalen, J., Deykin, D., Poller, L.: Oral Anticoagulants Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range. Chest ACCP Consensus Conference on Antithrombotic Therapy. *Chest*, Vol. 102(Suppl), pp. 312S-326S, 1992.
5. Hirsh, J., M.D., F.C.C.P.: Hamilton Civic Hospitals Research Center, Hamilton, Ontario, Personal Communication.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 U.S.A.

T1-B0001-04-05 Revised April 2005
Printed in U.S.A. 1170696A1

Shown in Product Identification Guide, page 309

EMSAM®

[em-sam]

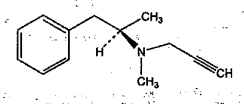
(SELEGILINE TRANSDERMAL SYSTEM)
CONTINUOUS DELIVERY FOR ONCE-DAILY APPLICATION
Rx only

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 (SSRIs 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-[(1R)-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:

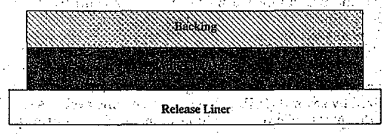


Selegiline Base

EMSAM systems are transdermal patches that contain 1 mg of selegiline per cm and deliver approximately 0.3 mg of selegiline per cm^2 over 24 hours. **EMSAM** systems are available in three sizes: 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2 that deliver, on average, doses of 6 mg, 9 mg or 12 mg, 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 anti-depressant 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 the 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 vitroreceptor binding assays, selegiline has demonstrated affinity for the human recombinant adrenergic α_{2B} receptor (K_i = 284 μM). No affinity [K_i >10 μM] was noted at dopamine receptors, adrenergic β_3, glutamate, muscarinic M_1–M_5, nicotinic, or roliprám receptor/sites.

Pharmacokinetics

Absorption

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 12 mg 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 5 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.

Continued on next page

Emsam—Cont.

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 6 mg/24 hours patch and a single, 10 mg oral immediate release dose of selegiline HCl in 12 healthy male and female volunteers.

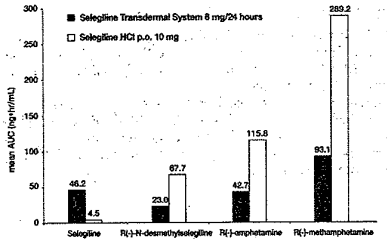
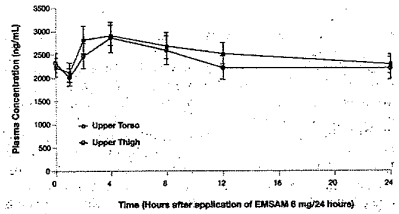


Figure 3: Average plasma (± 95% CI) selegiline concentrations in healthy male and female volunteers at steady-state after application of EMSAM (selegiline transdermal system) 6 mg/24 hours to the upper torso.



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 vitrowith 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 12 mg/24 hours 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** 6 mg/24 hours. (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** 6 mg/24 hours 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** 6 mg/24 hours 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 6 mg/24 hours selegiline patches for 10 days to the upper torso. Approximately 88%–89% of 6 mg/24 hours 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 6 and 8 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** 6 mg/24 hours 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 6 mg/24 hours, with possible increases to 9 mg/24 hours or 12 mg/24 hours 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** 6 mg/24 hours 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** (selegiline transdermal system) 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 hypersensitivity to selegiline or to any component of the transdermal system.

EMSAM is contraindicated with selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, and paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine); tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline); 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 (MAOIs e.g., isocarboxazid, phenelzine, and tranylcypromine) (see **WARNINGS**).

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

As with other MAOIs, **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 MAOIs, 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 MAOIs, **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** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours and 12 mg/24 hours, patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours**. (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 disorders.

Pooled analyses of short-term placebo-controlled trials of nine antidepressant drugs (SSRIs 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 nonpsychiatric. Although a causal link between the emer-

gence 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 healthcare providers. Such monitoring should include daily observation by families and caregivers. 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** (selegiline transdermal system) 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, MAOIs 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 6 mg/24 hours–12 mg/24 hours, 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** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours, and the results from the Phase I tyramine challenge study in fed volunteers administered **EMSAM** 12 mg/24 hours (see **PRECAUTIONS, Drug Interactions, *Tyramine***), patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours.**

If a hypertensive crisis occurs, **EMSAM** should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. Phentolamine 5 mg or labetalol 20 mg 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 9 mg/24 hours and 12 mg/24 hours

The following foods and beverages should be avoided beginning on the first day of **EMSAM** 9 mg/24 hours or 12 mg/24 hours treatment and should continue to be avoided for 2 weeks after a dose reduction to **EMSAM** 6 mg/24 hours or following the discontinuation of **EMSAM** 9 mg/24 hours or 12 mg/24 hours.

[See table above]

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 MAOIs 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 (SSRIs, e.g., fluoxetine, sertraline, paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine); tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline); oral selegiline or other MAOIs (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 MAOIs who were then given buspirone HCl.

After stopping treatment with SSRIs; SNRIs; TCAs; MAOIs; 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 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with **EMSAM**. At least 2 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 MAOIs, 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 10 mmHg 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** (selegiline transdermal system) be closely observed for postural changes in blood pressure throughout treatment. Dose increases should be made cautiously in patients with preexisting 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 oxcarbazepine 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 (SSRIs, e.g., fluoxetine, sertraline, paroxetine, and St. John's wort), dual serotonin and

Continued on next page

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.