National PBM Drug Monograph

Selegiline Transdermal System (EMSAM)

June 2007

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The purpose of VACO PBM_SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

Despite their efficacy, the monoamine oxidase inhibitors (MAOI) have fallen out of favor and are generally the last antidepressants to be considered. Their side effect profile, specifically requiring a tyramine-restricted diet, hypertensive crisis, and serotonin syndrome are reasons this class of antidepressants is avoided.

Selegiline is a MAOI that is selective for the enzyme monoamine oxidase B (MAO-B) at lower doses and a nonselective, irreversible inhibitor of MAO-A and -B at higher doses. Oral formulations of selegiline are currently available by prescription and labeled for use in the treatment of Parkinson's disease. The concept of an alternative route administration that would avoid inhibiting MAO-A in the gastrointestinal tract and liver, thus reducing the risk of tyramine-induced hypertension has been investigated via a transdermal selegiline delivery system.

Selegiline TDS is available in three strengths: 6 mg/24hours (20 mg/20 cm^2), 9 mg/24 hours (30 mg/30 cm^2) and 12 mg/24 hour (40 mg/40 cm^2). The recommended initial dose is 6 mg/24 hours with a new patch applied every 24 hours. The application site should be a dry, intact skin surface on the upper torso, upper thigh, or the outer surface of the upper arm and is to be rotated with each dose. Dose increases of 3 mg/24 should be made based upon the patient's response and no sooner than 2-week intervals. The maximum dose is 12 mg/24 hours.

Selegiline has demonstrated modest efficacy in three published placebo-controlled trials and one 52-week relapse prevention trial. Three of these trials did not require any dietary tyramine restriction. The safety of selegiline TDS was also assessed in these trials with application site reaction being the most common adverse event and the most common reason for discontinuation. There were no reports of hypertensive crisis.

Selegiline TDS carries the same contraindications and warnings as all other MAOIs with respect to drug-drug interactions. Patients taking the 9 mg and 12 mg/24 strengths are to observe a tyramine-restricted diet.

The cost for a selegiline transdermal patch is about $9.00.

Introduction[1-3]

Depression is one of the more common medical illnesses with a lifetime prevalence of up to 25%; affecting 32 to 35 million Americans. Initial pharmacotherapy for the treatment of depression includes the selective serotonin re-uptake inhibitors, serotonin-norepinephrine re-uptake inhibitors, bupropion and mirtazepine. Tricyclic antidepressants are generally reserved for severe depression and patients who have failed to tolerate or respond to other antidepressants. Despite their efficacy, the monoamine oxidase inhibitors (MAOIs) have fallen out of favor and are generally the last antidepressants to be considered. There side effect profile, specifically requiring a tyramine-restricted diet, hypertensive crisis, and serotonin syndrome are reasons this class of antidepressants is avoided. The MAOIs account for less that 1% of all antidepressant prescriptions.

Tyramine enters the body through two dietary sources: a product of the metabolism of tyrosine and the ingestion of fermented or aged foods in which tyrosine has already been broken down. Tyramine is structurally similar to norepinephrine (NE) and epinephrine, but with weaker adrenergic activity. Once tyramine is taken up by adrenergic neurons it displaces NE, thus dumping NE into the synaptic cleft leading to an increase in blood pressure, heart rate and perhaps hypertensive crisis. The body's normal defense against the absorption of tyramine is the enzyme monoamine oxidase A (MAO-A) in the gut and liver. Traditional MAOIs are irreversible inhibitors of MAO-A which requires 2-3 weeks to regenerate.

Selegiline is a MAOI that is selective for the enzyme monoamine oxidase B (MAO-B) at lower doses and a nonselective, irreversible inhibitor of MAO-A and -B at higher doses. Oral formulations of selegiline are currently available by prescription and labeled for use in the treatment of Parkinson's disease. The concept of an alternative route administration that would avoid inhibiting MAO-A in the gastrointestinal tract and liver, thus reducing the risk for tyramine-induced hypertension has been investigated via a transdermal selegiline delivery system. (See Drug-Food Interactions)

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues relevant to selegiline transdermal system (TDS) for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1,2]

The mechanism of action of MAOIs as antidepressants is not completely understood. In CNS neurons the MAOIs inhibit the enzyme monoamine oxidase which is responsible for the breakdown of the monoamine neurotransmitters norepinephrine, serotonin, dopamine and epinephrine. The initial effect is an accumulation of these neurotransmitters in the neuronal cytoplasm and synaptic cleft. After several weeks of treatment, down regulation of β-adrenoreceptors, $\acute{\alpha}_1$- and $\acute{\alpha}_2$-adrenoreceptors, and serotonin-1 and serotonin-2 receptors occurs and is believed to be in part responsible for their antidepressant effects.

Table 1: Pharmacokinetics of Selegiline TDS and Oral Tablets

Parameter	Selegiline TDS	Selegiline Oral Tablet
Metabolism	**Major**:CYP2B6, 2C9, 3A4/5 **Minor**: 2A6 **Principal metabolites**: R(-)-N-esmethylselegiline, R(-)-amphetamine, R(-)-methamphetamine	**Major**:CYP2B6, 2C9, 3A4/5 **Minor**: 2A6 **Principal metabolites**: N-esmethylselegiline, L(-)-amphetamine, L(-)-methamphetamine
Elimination	10% urine and 2% Feces as unchanged drug and metabolites	Not available
Half-life	Parent and metabolites: 18-35 hours (IV data)	Parent: 2 – 10 hours (parent)
Protein Binding	>90%	Not available
Bioavailability	25%-30% over 24 hours	Increased 3-4 fold by food

FDA Approved Indication(s) and Off-label Uses[1]

Selegiline TDS is indicated for the treatment of major depressive disorder.

Current VA National Formulary Alternatives

Tranylcypromine and phenelzine are the two oral MAOI antidepressants on the VANF; neither has a restriction or criteria for its use.

Dosage and Administration[1]

Selegiline TDS is available in three strengths: 6 mg/24hours (20 mg/20 cm^2), 9 mg/24 hours (30 mg/30 cm^2) and 12 mg/24 hour (40 mg/40 cm^2). The recommended initial dose is 6 mg/24 hours with a new patch applied every 24 hours. The application site should be a dry, intact skin surface on the upper torso, upper thigh, or the outer surface of the upper arm and is to be rotated with each dose. Dose increases of 3 mg/24 should be made based upon the patient's response and no sooner than 2-week intervals. The maximum dose is 12 mg/24 hours. As with any antidepressant, the duration of treatment with selegiline TDS is dependent on the patient's prior history and severity of depression.

The selegiline TDS consists of a matrix-type system composed of three layers: the inside release liner that is pealed away to reveal the middle adhesive drug layer and the outer backing layer containing the matrix system with occlusivity and physical integrity that protects the inner layer. The products inactive ingredients are acrylic adhesive, ethylene vinyl acetate/polyethylene, polyester, polyurethane, and silicone-coated polyester. The product does not contain latex. **The selegiline TDS is not to be cut.**

Special Populations
No dose adjustment is required for patients with mild to moderate renal or hepatic impairment. The recommended dose for patients age 65 years and older is 6 mg/24 hour and increases should be made with caution and patients closely monitored for postural changes in blood pressure.

Efficacy[4-7]

Efficacy Measures
The following instruments and scales were used in the clinical trials evaluating the efficacy of selegiline TDS and are considered standard in the assessment of antidepressants and other treatments of major depressive disorder.

Hamilton Rating Scale for Depression -17/21/28 (HAM-D-17/21/28, HRSD-17/21/28): The HAM-D is the most widely used observer-rated scale for the assessment of symptoms and severity of depression. The emphasis of the HAM-D-17 is on somatic symptoms, with the HAM-D-21 adding questions about diurnal variation, depersonalization, paranoia, and obsessive-compulsive symptoms. Additionally, the HAM-D-28 assesses symptoms of atypical depression.

Montgomery-Asberg Depression Rating Scale (MADRS): The MADRS is a 10 item scale focusing on the core symptoms of depression; 9 items are based on the patient's report and 1 item is the rater's observation.

Clinical Global Impression (CGI): This 3-item clinician-rated scale is used to measure the severity of illness (CGI-S), global improvement and efficacy index; repeated measures can assess response to treatment. When used in clinical trials, the CGI components are often analyzed separately as change from baseline.

Summary of efficacy findings
As of this writing, three clinical trials using selegiline TDS have been published and additional information on its efficacy and safety is available from transcripts posted on the FDA website and the products package insert. The following are inclusion and exclusion criteria consistent across all three trials:
Inclusion Criteria:

- Men and women ages 18 – 65 years

- Major depressive disorder, single or recurrent, per DSM-IV criteria
- A score of ≥20 on the HAM-D-17

Exclusion Criteria:

- Women who were pregnant or breastfeeding
- Potential subjects with any concurrent medical illness that could compromise safety or the study protocol, or affect interpretation of the study's findings
- The presence of a DSM-IV diagnosis Axis I disorder other than MDD (except for dysthymia).

The first published trial (Bodkin and Amsterdam, 2002) used a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose design with a one week, single-blind placebo run-in followed by a six-week treatment phase. Additional inclusion criteria included no greater than a 20% decrease in the HAM-D-17 or a score < 20 at the end of the placebo run in phase. Outcome measures were changed from baseline in HAMD-17 and -28 scores, MADRs, and CGI. Subjects were considered to have had a positive response if there was a 50% decrease or more on the HAMD-17 from baseline or an endpoint score of <8. A change to "much improved" or "very much improved" on the CGI was also considered a positive response. Additional efficacy analysis of questions in the HAMD about depressed mood and suicide were performed. The Medex Depression Evaluation Scale (MDES) was used to assess changes in sexual function. A sample size of 88 subjects per group was calculated based on a 3 unit change in the HAMD-17 and 80% power. Analysis was performed under intention-to-treat (ITT) and last observation carried forward (LOCF) conditions.

Following the placebo run-in phase, participants were randomly assigned to selegiline TDS 20 mg/20 cm^2 (6 mg/24 h) or placebo TDS to be applied each morning to rotating sites. Efficacy measures were taken at the end of weeks 1, 2, 3, 4, and 6. Safety measures assessed included ECG and orthostatic blood pressure and pulse. Subjects were instructed to follow a tyramine-restricted diet during the study and for the 2-weeks after treatment.

The number of subjects randomized to selegiline TDS or placebo were 89 and 88, respectively. There were no differences between groups at baseline with respect to demographics, HAMD, MADRS or CGI scores. Subjects ranged in age from 20 to 65 years, with the mean age being in the early 40's; 60% were women and >90% were Caucasian. The depressive episode was considered a single type for 36% and 29.5% randomized to selegiline TDS and placebo, respectively. For the ITT efficacy analysis, data were available for 88 subjects in each group.

After one-week of treatment the change from baseline in HAMD-17 and-28, and MADRS scores were statistically greater than those with placebo; these differences were sustained through six-weeks. The mean HAMD and MADRS scores at baseline and after 6-weeks are shown in Table 2. Significantly greater percentages of subjects receiving selegiline were considered to be responders or to have attained remission compared to placebo (Table 3).

Table 2. Primary Outcome Measures after Six Weeks

Measure	Selegiline Mean	Placebo Mean	P-value
HAMD-17			
Baseline	22.86	23.30	0.28
Week 6	14.13	18.37	0.01
HAMD-28			
Baseline	29.69	30.78	0.13
Week 6	18.37	23.19	0.004
MADRS			
Baseline	28.85	29.53	0.39
Week 6	19.09	23.84	0.005

Results of the CGI severity of illness scale also showed a significantly greater shift of subjects taking selegiline to normal, borderline- or mildly-ill ratings (58% combined) compared to placebo (35.2%). Forty-two percent of those receiving selegiline were noted to be "very much improved" or "much

improved" on the CGI improvement scale compared to 27.3% assigned to placebo. At the studies endpoint, scores on subscale items on the HAM-D for depressed mood improved significantly in the selegiline TDS group compared to placebo; there was no difference is the suicidality subscale score between the two groups, with both groups showing improvement.

By week 6, 11% of selegiline TDS subjects and 17% in the placebo group had dropped out; ineffectiveness was the most common reason in both groups, adverse events were responsible for 4 withdrawals in the selegiline TDS group and 5 in the placebo group; 3 in the selegiline TDS group dropped out due to application site reactions. Overall site reactions (erythemia, urticaria) were the most common adverse event reported, 36% selegiline TDS and 17% placebo (p=.006). The duration of site reactions was "several days;" 5 subjects in the selegiline TDS group required treatment. The mean changes in orthostatic blood pressure were not considered clinically significant although they were greater in the selegiline TDS subjects, -2.3 mm Hg compared to -0.8 mm Hg with placebo. There were no clinically relevant ECG changes in either group. No hypertensive episodes were noted. Sexual function was found to improve in the selegiline TDS subjects compared to those assigned to placebo.

The authors concluded that selegiline TDS was superior to placebo on all measures of efficacy. The limitations of this study include only a 6-week duration and fixed-dose design. The trial length was insufficient to draw conclusions about sexual side effects. It was the only trial to require a tyramine-restricted diet.

A second trial (Amsterdam, 2003) evaluated the safety of transdermal selegiline 20 mg/20 cm^2 (6 mg/24 h) without dietary tyramine restrictions. Outcome measures included the MADRS, HAM-D-28 and HAM-D-17 as well as CGI-S, CGI-change, percent responding based on a >50% decrease from baseline in the HAM-D-17/28 score. Subjects were evaluated on weeks 1, 2, 3, 4, 6 and 8. A sample size of 125 subjects per group was required to detect a mean change of 2.5 on the HAM-D-17/28 from baseline after 8-weeks with 80% power. Analysis was done using an ITT with LOCF approach. A total of 316 subjects with moderate-severe MDD (HAM-D $\geq$20) enrolled in the trial, with 301 randomized to selegiline TDS (n=149) or placebo TDS (n=152) after a 1-week placebo run-in phase. Of those randomized, 289 remained on treatment long enough for at least one evaluation and were included in the efficacy analysis. Ninety-eight percent of participants completed the trial.

The subjects studied were primarily women (~64%), white (>75% in both groups) and with a mean age of between 41 and 43.5 years. Nearly two-thirds experienced recurrent depression with a mean HAM-D-17 score of 22.8. There were no significant differences between the group demographics. The mean MADRS score differed significantly in favor of selegiline TDS compared to placebo at weeks 4, 6 and 8 as it did with the mean HAM-D-28 at week 8. At no time during the study was there a significant between group difference in HAM-D-17 score, nor was there a difference in the percent of subjects responding in either treatment arm (Table 3), or demonstrating a significant difference in any of the secondary outcome measures (CGI-S, CGI-change).

Adverse events were significantly more common in the selegiline TDS subjects due application site reactions: TDS, 31.5% versus placebo, 15.1%. Five subjects in the TDS discontinued the study due a site reaction compared to none in the placebo group. Cardiovascular events were less than or equal to 4% in both groups and equal between groups and without clinical significance. No episodes of hypertensive crisis were reported and there was no difference between the groups, or from baseline with respect to sexual side effects.

The authors concluded that compared to placebo, selegiline TDS may have a modest, but statistically significant, antidepressant benefit and a similar safety profile in the absence of a tyramine-restricted diet.

The fixed dose design of this trial does not answer the question of whether a dose-response relationship exists. The 8-week study duration is insufficient time to evaluate selegiline TDS's sexual side effect profile.

The third trial (Feiger, et al., 2006) also was conducted without dietary tyramine restriction and used a flexible dosing regimen allowing the dose of selegiline TDS to be titrated from an initial dose of 6 mg/24h to 9 mg/24h or 12 mg/24h based on clinician's impression of response after 2, 3, and 5 weeks; the higher doses could also be lowered if not tolerated. The placebo TDS dose was adjusted in a similar manner. A calculated sample size of 125 subjects per group was necessary to provide 80% to detect a between group difference of ~3.5 units in mean change from baseline in HAM-D-28 scores. A total of 265 subjects were randomized to selegiline TDS (n=132) or placebo (n=133) with 100 and 106 subjects completing the 8-week trial in the selegiline TDS and placebo groups, respectively. The final dose distribution for all those randomized was as follows: 6 mg/24h: TDS 15%, placebo 16%; 9 mg/24h: TDS 39%, placebo 23%; and 12 mg/24h: TDS 46%, placebo 61%. Seven subjects in the TDS group and 5 in the placebo group had their dose lowered after it had been increased. The trial primary outcome variable was change from baseline on the HAM-D-28; secondary outcome measures were the MADRS, the Inventory for Depression Symptomatology-Self Rated (IDS-SR), HAM-D-17, and CGI-change.

Baseline demographics revealed that over 80% of participants were white and over 50% were women. Over 70% had recurrent major depression with mean HAM-D-28 scores of 28.3 and 28.6 for the selegiline TDS and placebo groups, respectively. Pretreatment CGI scores were all either moderately or markedly ill, with one subject severely ill. Ninety-six percent of the selegiline TDS group and 89% of subjects in the placebo group were considered to be compliant. By Week-5 a statistically significant improvement was noted on the mean HAM-D-28 (p=0.03) and MADRS scores (p=0.02)for the selegiline TDS group compared with placebo. These differences were maintained at Week-8 at which time the IDS-SR (p=0.03) also separated from placebo. At Week-8 the mean decrease in HAMD-D-28 was 11.1 in the selegiline TDS group compared to 8.9 in the placebo group; mean total scores were 17.2 and 19.8, respectively. At no time was there a significant difference between the treatment groups on the HAM-D-17 score. Response rates based on the HAM-D-28 did not differ significantly (Table 3).

Thirty-two subjects in the selegiline TDS arm and 27 in the placebo arm discontinued the study after randomization. The principal reasons for leaving early were "lost to follow-up" (n=16) and adverse drug events (n=12). Among subjects receiving selegiline TDS, application site reaction (2), insomnia (1), and feeling nervous (1) were cited, while insomnia (1), dizziness (2), and feeling nervous (1) were cited by the placebo group; other single incident reasons for discontinuation were not provided.

The authors concluded that selegiline TDS demonstrated short-term efficacy, safety, and tolerability over the dose range of 6 mg to 12 mg/24 hours in patients with MDD.

Table 3. Response and Remission Rates

Study	Dose	Duration	Results		
Bodkin & Amsterdam,2002	6 mg/24 h (20 mg/cm^2)	6 weeks	Response HAM-D-17/28 Remission HAM-D-17	TDS 37.5% 22.7%	Placebo 22.7% 11.4%
Amsterdam, 2003	6 mg/24 h (20 mg/cm^2)	8 weeks	Response MADRS HAM-D-17 HAM-D-28	 33.1% 32.4% 32.4%	 20.8% 27.8% 29.2%
Feiger, et al., 2006	6 , 9, or12 mg/24 h (flexible dose)	8 weeks	Response HAM-D-28	 40%	 30%

Response: ≥50% reduction it total score after 6-weeks
Remission: Total score <8 after 6-weeks

A summary of a 52-week, multicenter, double-blind, placebo controlled, relapse prevention trial was obtained from the manufacturer of selegiline TDS. This trial has been presented to the FDA and at national meetings. Initially using an open-label design 675 outpatients with MDD (HAM-D-17 ≥18) received selegiline TDS 20 mg/cm^2 (6 mg/24h) for 10 weeks; patients who responded (HAM-D-17 ≤10; n=342) were then randomized to continue selegiline TDS 20 mg/cm^2 (n=158) or placebo (n=163) for up to 52 weeks. The primary outcome measure was relapse defined as a HAM-D-17 ≥14; a CGI-S ≥3, with a ≥2

point increase from double-blind baseline; and meeting DSM-IV criteria for MDD. During the trial participants were under no dietary tyramine restrictions and were not permitted to take medication known to interact with MOAIs.

Approximately 52% of subjects in both groups discontinued treatment by week 12 of the double-blind portion of the study. After both 6-months and 1-year, 16.8% of patients randomized to selegiline TDS had experienced a relapse compared to 29.4% and 30.7% of placebo-treated patients, (p=0.005 and p=0.003) respectively. The time to relapse was significantly longer in the selegiline TDS-treated patients compared to placebo (Kaplan-Meir: p=0.0012 at 6 months and p=0.006 at 1 year).

Treatment emergent adverse events were reported in 54.4% of selegiline TDS-treated patients and 41.7% of placebo-treated patients during the double-blind phase of the study. A total of 13.2% selegiline TDS- and 6.7% placebo-treated patients discontinued the study due to an adverse event. There were no acute hypertensive changes, drug-related ECG changes, or significant differences between groups in the incidence of cardiovascular adverse events.

Adverse Events (Safety Data)[1, 3-7]

Tyramine-challenge Studies
The manufacturer of selegiline TDS conducted 14 tyramine-challenge studies with objective of providing a clinically relevant measure of the degree of MAO-A inhibition as reflected by the estimated dose of tyramine (mg) required to produce a 30 mmHg in systolic blood pressure (TYR30). The lower the TYR30, the greater the degree of MAO-A inhibition. Previous studies have shown a tyramine-rich meal contains no more that 40 mg of tyramine.

The study design included a baseline phase during which subjects received fixed escalating doses of tyramine in the fasting or fed state for 3 days in order to determine the TYR30. Subjects then received an MAOI (selegiline TDS 20 mg. 30 mg, or 40 mg/day; selegiline oral 5 mg twice a day; or tranylcypromine 30 mg per day) for 8 to 30 days. After the specified time exposed to an MAOI, subjects were again given increasing doses of tyramine in order to determine their on-drug TYR30.

As shown in Table 3, the mean baseline fasting TYR30 ranged from 400 to 588 mg. After exposure to selegiline TDS for 9-10 days the mean TYR30 decreased to ~200-300 mg with an inverse relationship between selegiline TDS dose and TYR30. Duration of exposure to selegiline TDS also decreased the TYR30. This time-dependency factor was greater with the 40 mg/day patch of selegiline than the 20 mg/day patch. The change in TYR30 with oral selegiline 5 mg twice a day was less than with selegiline TDS, while only 10 mg of tyramine was necessary to produce a 30 mmHg increase in systolic blood pressure following 8 days of oral tranylcypromine. One study included duration of exposure to selegiline TDS out to 60 and 90 days found that after 30 days the TYR30 leveled off.

Table 3. Tyramine-challenge Studies: Fasting mean TYR30

Drug (N)	Dose/day x Duration	Baseline TYR30 (mg)	On-drug TYR30 (mg)
Selegiline TDS (47) (3 study pool)	20 mg x 9-10 days	507	298
Selegiline TDS (12)	20 mg x 30 days	483	204
Selegiline TDS (10)	30 mg x 10 days	470	210
Selegiline TDS (12)	40 mg x 10 days	588	198
Selegiline TDS (18)	40 mg x 30 days	575	84
Selegiline po (21)	5 mg BID x 9 days	529	357
Tranylcypromine (9)	30mg x 8 days	400	10

Although limited data are available, only for the 40 mg selegiline TDS dose, it appears that the meanTYR30 increases when tyramine is taken with food: Fasting 64 mg (47-128 mg) and non-fasting 172 mg (95-249 mg).

One cautionary note is that the range for TYR30 demonstrates inter-individual variation. For example, the minimum TYR30 with the 20 mg and 40 mg selegiline TDS doses were 50 mg and 25 mg, respectively.

Deaths and Other Serious Adverse Events (optional)
There were no deaths or other life-threatening events including hypertensive crisis attributed to selegiline TDS in the clinical trials.

Table 4. Common Adverse Events

*Adverse Event	Bodkin & Amsterdam, 2002 As reported by ≥5%		Amsterdam, 2003 As reported by ≥3%		Feiger, et al, 2006 As reported by ≥10%	
	TDS (n=89)	Placebo (n=88)	TDS (n=149)	Placebo (n=152)	TDS (n=132)	Placebo (n=133)
Any	78 (87.6%)	69 (78.4%)	93 (62.4)	76 (50.0)	105 (80)	98 (74)
Body as a whole	40 (44.9)	36 (40.9)	25 (16.8)	34 (22.4)	NR	NR
Headache	20 (22.5)	19 (21.6)	17 (11.4)	19 (12.5)	NR	NR
Infection	8 (9.0)	2 (2.3)	NR	NR	18 (14)	17 (13)
Pain	4 (4.5)	6 (6.8)	NR	NR	NR	NR
Back pain	5 (5.6)	3 (3.4)	NR	NR	NR	NR
Abdomin. pain	3 (3.4)	5 (5.7)	1 (0.7)	6 (4.0)	NR	NR
Asthenia	NR	NR	5 (3.4)	5 (3.3)	NR	NR
Cardiovascular	3 (3.4)	6 (6.8)	6 (4.0)	4 (2.6)	NR	NR
Hypertension	0	1 (1.1)	NR	NR	NR	NR
Postural hypo.	1 (1.1)	2 (2.3)	NR	NR	NR	NR
Palpitations	0	1 (1.1)	NR	NR	NR	NR
Tachycardia	1 (1.1)	0	NR	NR	NR	NR
Skin	39 (43.8)	21 (23.9)	56 (37.6)	26 (17.1)	NR	NR
Application site reaction	32 (36.0)	15 (17.0)	47 (31.5)	23 (15.1)	53 (40)	27 (20)
Rash	NR	NR	5 (3.4)	1 (0.7)	NR	NR
Nervous	25 (28.1)	28 (31.8)	29 (19.5)	34 (22.4)	13 (10)	8 (6)
Dizziness	7 (7.9)	5 (5.7)	6 (4.0)	4 (2.6)	17 (13)	9 (7)
Insomnia	6 (6.7)	6 (6.8)	11 (7.4)	6 (4.0)	40 (30)	19 (14)
Somnolence	6 (6.7)	4 (4.5)	3 (2.0)	5 (3.3)	NR	NR
Depression	1 (1.1)	5 (5.7)	NR	NR	NR	NR
Anxiety	NR	NR	1 (0.7)	7 (4.6)	NR	NR
Digestive	23 (25.8)	26 (29.5)	19 (12.8)	20 (13.2)	NR	NR
Diarrhea	8 (9.0)	9 (10.2)	8 (5.4)	9 (5.9)	13 (10)	5 (4)
Dry mouth	8 (9.0)	6 (6.8)	8 (5.4)	8 (5.3)	16 (12)	10 (8)
Flatulence	5 (5.6)	2 (2.3)	NR	NR	NR	NR
Dyspepsia	3 (3.4)	6 (6.8)	2 (1.3)	5 (3.3)	NR	NR
Nausea	NR	NR	6 (4.0)	6 (4.0)	NR	NR
Metabolic & nutritional	NR	NR	5 (3.4)	6 (4.0)	NR	NR
Respiratory	14 (15.7)	16 (18.2)	5 (3.4)	4 (2.6)	NR	NR
Pharyngitis	5 (5.6)	7 (8.0)	NR	NR	NR	NR
Sinusitis	5 (5.6)	1 (1.1)	NR	NR	NR	NR
Rhinitis	4 (4.5)	6 (6.8)	NR	NR	NR	NR
Urogenital	12 (13.5)	10 (11.4)	3 (2.0)	5 (3.3)	NR	NR
UTI	6 (6.7)	5 (5.7)	NR	NR	NR	NR
Musculoskeletal	4 (4.5)	7 (8.0)	NR	NR	NR	NR
Myalgia	2 (2.2)	5 (5.7)	NR	NR	NR	NR
Special Sense	NR	NR	9 (6.0)	6 (4.0)	NR	NR

*All adverse events categorized by the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) body system.
NR – not reported.

Other Adverse Events

No adequately designed studies of selegiline TDS's effect on sexual dysfunction have been conducted. In the placebo-controlled clinical trials, the incidence of sexual side effects with selegiline was <1% in men (n=304) and 0% in women (n=513) and <1% in men (n=256) and women (n=412) with placebo.

Weight gain and weight loss were reported in both patients assigned to selegiline TDS and placebo in the clinical trials. The mean change in body weight in selegiline TDS treated patients was -1.2 pounds versus +0.3 pounds in those treated with placebo.

Tolerability
Selegiline TDS appeared to be as well tolerated as placebo in the three clinical trials. Twenty-three of the 370 subjects (6.2%) randomized to selegiline TDS dropped-out of clinical trials due to an adverse event compared to 16 of the 373 subjects (4.3%) n the placebo groups. An application site reaction was the most common reason for discontinuation.

Precautions/Contraindications[1]

Warnings
- As with all antidepressants, selegiline TDS has a black box warning regarding increased suicidaility in children and adolescents and warning regarding clinical worsening and/or the emergence of suicidality in adults.
- Clinicians are advised to screen patients for signs, symptoms or a history of bipolar disorder prior to prescribing selegiline TDS
- Not for use in patients with pheochromocytoma.
- At least 2-weeks should elapse after stopping selegiline TDS before starting a new antidepressant or any other drug that is contraindicated with selegiline TDS.

Precautions
- Orthostatic hypotension is a known adverse effect of oral MAOIs and can occur with selegiline TDS. In clinical trials the incidence of orthostatic hypotension was 9.8% in patients treated with selegiline TDS compared to 6.7% treated with placebo.
- In geriatric patients participating in the clinical trials (n=198), patients age of 50 years and older appeared to be at a higher risk for rash than younger patients.
- Activation of mania or hypomania can occur with any antidepressant. A total of 8 out of 2036 (0.4%) patients treated with selegiline TDS in the clinical trials experienced a manic episode. Selegiline TDS should be use cautiously in patients with a history of bipolar disorder.
- Use of selegiline TDS in patient with concomitant illness has not been extensively studied. Caution is advised.
- Selegiline is Pregnancy Category C
- It is unknown whether selegiline is excreted in human breast milk and caution is advised if administering to a nursing mother.

Contraindications
- Patients with a known hypersensitivity to selegiline
- Concurrent use of other antidepressants or use of other antidepressants within a period of 4 to 5 half-lives (usually 2-weeks, 5-weeks for fluoxetine).
- Concurrent use with
  - Meperidine, tramadol, methadone, and propoxyphene
  - Dextromethorphan
  - St. John's Wort
  - Cyclobenzaprine
  - Oral selegiline or other MAOIs
  - Carbamazepine or oxcarbazepine
  - Buspirone
  - Amphetamines, pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine
- Patients undergoing elective surgery requiring general anesthesia are to discontinue selegiline TDS at least 10 days prior to surgery. They are also to avoid cocaine and local anesthetics containing a vasoconstrictor. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name selegiline transdermal: selegiline oral tablets, sertraline, other transdermal products including scopolamine, fentanyl, and nitroglycerin.

LA/SA for trade name EMSAM: EMLA, Emcyt, SAM-E, Emcin clear (swab), Emko foam, Emgel

Drug Interactions[1,2]

Drug-Drug Interactions
Selegiline TDS is an MAOI and the same extensive list of drug-drug interactions applies as with any other MAOI.

Pharmacokinetic Interactions

- Barbiturates – MAOIs may prolong the effects of barbiturates
- Cytochrome 2B6 inducers – decrease selegiline concentrations and effect
- Cytochrome 2B6 inhibitors – increase selegiline concentrations and effect
- Oral contraceptives – may increase selegiline concentrations

Risk for Life-Threatening Adverse Reaction (Hypertensive Crisis or Serotonin Syndrome)

- Amphetamines
- Buspirone
- COMT inhibitors
- Guanethidine and guanadrel
- Reserpine
- Anorexiants – sibutramine, dexfenfluramine, fenfluramine
- CNS stimulants
- Dextromethorphan
- Decongestants such as pseudoephedrine, phenylephrine
- All antidepressants
- St. John's Wort
- Buspirone
- Meperidine, tramadol, methadone, and propoxyphene

The manufacturer has specifically studied and reported on selegiline TDS taken in combination with the following medications:

- Alcohol did not affect the pharmacokinetics or pharmacodynamics of selegiline TDS and visa versa. Patients are to be advised to that the use of alcohol with selegiline TDS is not advised.
- Alprazoloam 15 mg/day (a CYP3A4/5 substrate) did not affect the pharmacokinetics of selegiline TDS 6 mg/24 hours taken for days, nor did selegiline TDS affect alprazolam's pharmacokinetics.
- 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 selegiline 6 mg/per 24 hours in subjects who had received carbamazepine (400 mg/day) for 14 days. Changes in plasma selegiline concentrations were nearly 2-fold, and variable across the subject population. The clinical relevance of these observations is unknown. Carbamazepine is contraindicated with MAOIs, including selegiline.
- Ibuprofen, a CYP2C9 substrate (800 mg single dose), coadministration did not affect the pharmacokinetics of either selegiline 6 mg per 24 hours for 11 days or ibuprofen.

- Ketoconazole: Seven-day treatment with ketoconazole (200 mg/day), a potent inhibitor of CYP3A4, did not affect the steady-state pharmacokinetics of selegiline in subjects who received selegiline 6 mg per 24 hours for 7 days, and no differences in the pharmacokinetics of ketoconazole were observed.
- Levothyroxine: In healthy subjects who had received selegiline 6 mg per 24 hours for 10 days, single-dose administration with levothyroxine (150 mcg) did not alter the pharmacokinetics of either selegiline or levothyroxine (as judged by triiodothyronine and thyroxine plasma levels).
- Olanzapine: In subjects who had received selegiline 6 mg per 24 hours for 10 days, coadministration with olanzapine, a substrate for CYP1A2, CYP2D6, and possibly CYP2A6, did not affect the pharmacokinetics of either selegiline or olanzapine.
- Phenylpropanolamine: In subjects who had received selegiline 6 mg per 24 hours for 9 days, coadministration with phenylpropanolamine (25 mg every 4 hours for 24 hours)did not affect the pharmacokinetics of phenylpropanolamine. There was a higher incidence of significant blood pressure elevations with the coadministration of selegiline transdermal and phenylpropanolamine than with phenylpropanolamine alone, suggesting a possible pharmacodynamic interaction. It is prudent to avoid the concomitant use of sympathomimetic agents with selegiline.
- Risperidone: In subjects who had received selegiline 6 mg per 24 hours for 10 days, coadministration with risperidone (2 mg per day for 7 days), a substrate for CYP2D6, did not affect the pharmacokinetics of either selegiline or risperidone.

Other Drug Interactions

- Disulfiram taken in combination with an MAOI has been associated with delirium
- Lithium taken in combination with an MAOI may result in hyperpyrexia
- Hypoglycemic agents in combination with an MAOI have been reported to increase the risk of hypoglycemic episodes

Drug-Food Interactions[1]

Consumption of tyramine-containing foods while taking an MAOI may result in hypertensive crisis. The 9 mg and 12 mg/24 hour strengths of selegiline TDM require dietary modifications to restrict the amount of tyramine consumed. Foods and beverages rich in tyramine are to be avoided and include, but are not limited to the following:

- Air dried, aged and fermented meats including sausages and salamis
- Pickled herring
- Improperly stored or spoiled meat, fish or poultry
- Broad bean pods such as fava beans
- Aged cheeses
- Tap and non-pasteurized beers
- Concentrated yeast extract, sauerkraut, most soybean products (including tofu and soy sauce, but excluding soy milk)

Drug-Lab Interactions

None reported.

Acquisition Costs

Table 5: MAOI Cost per Day and Per Year

Drug	Dose	Cost/Day/patient ($)	Cost/Year/patient ($)
Selegiline transdermal	6 mg/24 hours 9 mg/24 hours 12 mg/24 hours	9.06 9.35 9.29	3307 3413 3391
Phenelzine	60 mg/day	1.42	519
Tranylcypromine	30 mg/day	1.43	521

Pharmacoeconomic Analysis

There have been no pharmacoeconomic studies of this product.

Conclusions

From a safety perspective, the information available suggests that selegiline TDS lowers the risk of tyramine-induced hypertensive crisis despite the labeling requirement for a tyramine restricted diet with the 9 mg and 12 mg per 24 hour patches. The TDS formulation is not anticipated to lower the risk of serious life-threatening adverse effects due to drug-drug interactions. As to the efficacy of selegiline TDS, modest response rates of 33% to 40% were reported in clinical trials compared to 22% to 30% with placebo. A narrow difference between placebo and active agent is not inconsistent with antidepressant trials. The majority of trial participants suffered from recurrent depression. Selegiline TDS did demonstrate a difference from placebo in relapse rates in the only long term study conducted. Still there are no comparative trials to other MAOIs or antidepressants from other classes and no information on selegiline TDS's efficacy in refractory patients. All of these absences limit one's ability to decide on selegiline TDS's place in the treatment of major depressive disorder.

References:

1. EMSAM (selegiline transdermal system) package insert, February 2006
2. Semla TP, Beizer JL, Higbee MD. Geriatric Dosage Handbook, 12th ed., Lexi-Comp, Inc., Hudson, OH, 2007.
3. Transcript, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Psychopharmacology Drug Advisory Committee, VII, October 26, 2005, Gaithersburg, MD.
4. Bodkin JA, Amsterdam JD. Transdermal selegiline in major depression: A double-blind, placebo-controlled, parallel-group study in outpatients. Am J Psychiatry 2002; 159:1869-75.
5. Amsterdam JD. A double-blind, placebo-controlled trial of the safety and efficacy of selegiline transdermal system without dietary restrictions in patients with major depressive disorder. J Clin Psychiatry 2003; 64:208-14.
6. Feiger AD, Rickels K, Rynn MA, et al. Selegiline transdermal system for the treatment of major depressive disorder: An 8-week, double-blind, placebo-controlled, flexible-dose titration trial. J Clin Psychiatry 2006; 67:1354-61.
7. Personal Communication, A. Sharma, Pharm.D., Somerset Pharmaceuticals, November 8, 2006.

Contact person: Todd Semla, MS, Pharm.D., BCPS, FCCP, AGSF, VACO PBM, Hines, IL