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Selegiline Transdermal System
In the Treatment of Major Depressive Disorder

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Abstract

▲ The monamine oxidase (MAO) inhibitor selegiline is selective for MAO-B at the low oral dosages used in the treatment of Parkinson's disease. However, MAO-A is also inhibited at the high oral dosages needed to effectively treat depression (not an approved indication), necessitating a tyramine-restricted diet. The selegiline transdermal system was designed to deliver antidepressant drug concentrations to the CNS, without substantially impairing small intestine MAO-A activity. At the target dose of 6 mg/24 hours, tyramine dietary restrictions are not needed.

▲ Short-term treatment with fixed (6 mg/24 hours) or flexible (6, 9 or 12 mg/24 hours) doses of selegiline transdermal system was superior to placebo on most measures of antidepressant activity in 6- or 8-week, randomised, double-blind, multicentre studies in adult outpatients with major depressive disorder (MDD).

▲ Likewise, long-term treatment with a fixed dose of selegiline transdermal system 6 mg/24 hours was superior to placebo as maintenance therapy in a 52-week, randomised, double-blind, multicentre, relapse-prevention trial in patients with MDD.

▲ Selegiline transdermal system therapy was generally well tolerated in placebo-controlled studies; application site reactions, mostly of mild to moderate severity, were the most commonly reported adverse events. The incidence of sexual adverse effects and weight gain was low and similar to that with placebo.

Features and properties of selegiline transdermal system (EMSAM®)	
Indication	
Major depressive disorder	
Mechanism of action	
Irreversible monoamine oxidase (MAO) inhibitor thought to potentiate the activity of serotonin, noradrenaline (norepinephrine) and dopamine	
Dosage and administration	
Recommended starting/target (maximum) dosage	6 mg/24 hours (12 mg/24 hours)
Frequency of administration	Once daily
Route of administration	Transdermal
Pharmacokinetic profile (mean pharmacokinetic parameters for selegiline following a single, 24-hour application of a selegiline transdermal system 6 mg/24 hours patch in 12 healthy male volunteers)	
Peak plasma concentration	2162 pg/mL
Time to peak plasma concentration	18.4h
Area under the plasma concentration-time curve from time zero to infinity	46 162 pg • h/mL
Plasma elimination half-life	20.1h
Most common adverse events	
Application site reactions, headache, insomnia, diarrhoea and dry mouth	

Major depressive disorder (MDD) is a highly prevalent and disabling condition.[1] It has a lifetime prevalence of ≈16% in the US;[2] worldwide, it is the leading cause of non-fatal disease burden (accounting for 12% of all years lived with disability) and the fourth leading cause of total disease burden (accounting for 4.4% of all disability-adjusted life-years).[3] Treatment modalities include psychotherapy, pharmacotherapy, combined psychopharmacotherapy or electroconvulsive therapy (ECT). Of these, pharmacotherapy is the preferred choice for moderate-to-severe episodes of depression, about half of which will show improvement.[4]

Irreversible monoamine oxidase (MAO) inhibitors, the first antidepressant drugs to be introduced, enhance central monoaminergic neurotransmission by preventing the degradation of (all) monoamines within the presynaptic terminal.[1,5] These agents are effective in the treatment of MDD, but are limited by relatively poor tolerability, the requirement for divided daily dosing, the potential for adverse drug-drug interactions and, due to significant MAO-A inhibition in the small intestine, the need to impose tyramine dietary restrictions in order to avoid hypertensive reactions associated with ingestion and absorption of this vasoactive amine ('cheese effect').[1,4,6-8] With the advent of other antidepressants, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and the atypical agent buproprion, these limitations have seen MAO inhibitors relegated to second-, third- and even fourth-line treatment.[1,5,9] Nonetheless, their efficacy, in particular for atypical and treatment-resistant depressions, is recognised in current (2000) guidelines[7,8] and sustains interest in this drug class. The search for a safer, better tolerated and more convenient MAO inhibitor has therefore continued.[5,9]

Selegiline is an irreversible inhibitor of MAO, which has greater affinity for MAO-B over MAO-A.[10] The low oral dosage approved in the adjunctive treatment of Parkinson's disease produces selective inhibition of MAO-B (and therefore does not necessitate dietary tyramine restrictions), whereas higher oral dosages, which are effective in the treatment of depression (not an approved indication), inhibit both MAO-B and MAO-A (and hence necessitate dietary tyramine restrictions).[6]

The selegiline transdermal system (EMSAM®)[1] is a transdermal formulation of selegiline designed to provide brain levels of the drug sufficiently high to inhibit MAO-A and -B activity in the CNS and produce an antidepressant effect, without substantially impairing MAO-A activity in the small intestine, thereby avoiding the need for dietary tyramine modifications at the starting and target dose (6 mg/24 hours).[11] The pharmacological properties, clinical efficacy and tolerability of the selegiline transdermal system are the subject of this profile.

Selegiline transdermal system patches are available in three sizes.[12] The 20 mg/20 cm^2, 30 mg/30 cm^2 and 40 mg/40 cm^2 patches deliver, on average, 6, 9 and 12mg, respectively, of selegiline over a 24-hour period[12] (hereafter referred to as the 6, 9 and 12 mg/24 hours patches, respectively).

1. Pharmacodynamic Profile

- The mechanism of antidepressant activity of selegiline is not fully understood,[12] but appears to involve inhibition of brain MAO activity, resulting in the potentiation of serotonergic, noradrenegic and dopaminergic activity. In an *in vivo* animal model (rodent forced swim test), daily transdermal selegiline administration demonstrated antidepressant-like activity only at doses which inhibited both MAO-A and -B activity in the CNS.[13]
- In another *in vivo* animal model, daily transdermal selegiline administration, unlike oral dosing, preferentially inhibited MAO-A activity in the brain relative to that in the liver and intestinal epithelium.[14] Moreover, transdermal delivery of selegiline was six to eight times more potent than oral dosing as an inhibitor of brain MAO-A activity.[14]

2. Pharmacokinetic Profile

- Mean values for selegiline peak plasma concentration, time to peak plasma concentration and area

1 The use of trade names is for product identification purposes only and does not imply endorsement.

under the plasma concentration-time curve from time zero to infinity were 2162 pg/mL, 18.4 hours and 46 162 pg • h/mL, respectively, following application of a single selegiline transdermal system 6 mg/24 hours patch in 12 healthy male volunteers.[15] Compared with selegiline administered orally (which is subject to extensive hepatic first-pass metabolism), the pharmacokinetic profile of selegiline administered via the selegiline transdermal system is characterised by greater plasma exposure to selegiline, but less plasma exposure to selegiline metabolites (figure 1).[15]

- Steady-state plasma selegiline concentrations were achieved after ≈5 days in a multiple-dose trial in six healthy male volunteers.[16] Of note, the selegiline transdermal system patches evaluated in this study contained 1.8mg of selegiline per cm^2, whereas selegiline transdermal system patches approved for use in the US contain 1mg of selegiline per cm^2.[12]
- Selegiline is ≈90% bound to plasma proteins over the concentration range 2–500 ng/mL.[12]
- Selegiline is neither accumulated[12] nor metabolised[17] in human skin. However, it is extensively metabolised in the liver to *N*-desmethylselegiline or R-(-)metamfetamine, which are further metabolised to R-(-)amfetamine. These metabolites are all levorotatory *l*-enantiomers; no racemic biotransformation to the more pharmacologically active dextrorotatory form *d*-enantiomers occurs.[12]
- Several cytochrome P450 (CYP) isoenzymes are involved in the hepatic metabolism of selegiline and its metabolites, including CYP2A6, CYP2B6, CYP2C9 and CYP3A4/5.[12]
- Mean values for selegiline renal clearance and plasma elimination half-life were 0.639 L/h and 20.1 hours, respectively, following a single, 24-hour application of a selegiline transdermal system 6 mg/24 hours patch in 12 healthy male volunteers.[15] Approximately 10% of a dermally applied radiolabeled dose of selegiline was recovered in the urine; ≈2% was recovered in the faeces. The remainder of the applied dose was either unabsorbed (63%) or unaccounted for (25%). Of the dose recovered in the urine, 99.9% was in the form of selegiline metabolites.[12]
- The pharmacokinetics and metabolism of selegiline administered via the selegiline transdermal system are not affected by gender, the presence of mild or moderate hepatic impairment, or the presence of mild, moderate or severe renal impairment.[12] Hence, dosage adjustments are not required on the basis of gender or in patients with hepatic impairment (moderate) or renal dysfunction.[12]
- The effect of age on the pharmacokinetics and metabolism of selegiline administered via the selegiline transdermal system have not been studied systematically; the recommended dose for elderly patients is 6 mg/24 hours.[12]

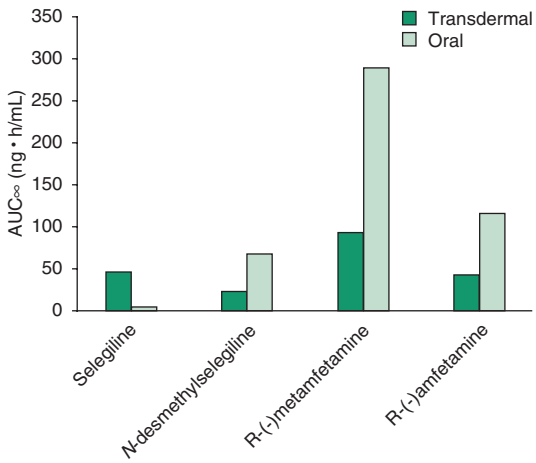

Fig. 1. Exposure to selegiline and its major metabolites. Area under the plasma concentration-time curve from time zero to infinity (AUC_∞) for selegiline and its major metabolites following application of a single selegiline transdermal system 6 mg/24 hours patch or oral administration of a single immediate-release dose of selegiline HCl 10mg in a randomised, crossover study in 12 healthy male volunteers. Data derived from Ziemniak et al.[15]

Tyramine Drug Interaction Studies

- In tyramine challenge crossover studies in fasting healthy male volunteers (n = 10–24),[18] selegiline transdermal system 6 mg/24 hours for up to 33 days did not cause clinically significant increases in tyramine sensitivity, suggesting that dietary restrictions are not necessary in patients treated with this formulation/dosage.[18]

- Expressed as the mean tyramine sensitivity factor (TSF; i.e. the ratio of tyramine doses required to achieve a sustained ≥30mm Hg increase above baseline in systolic blood pressure before vs during active treatment), the increase in tyramine sensitivity after 9 or 10 days' treatment with selegiline transdermal system 6 mg/24 hours was >20 times less than that after 8 days' treatment with a standard oral dosage of the irreversible MAO-inhibitor tranylcypromine (30 mg/day) [1.86 vs 40.0; n = 10] and similar to that after 9 days' treatment with the US FDA-approved oral dosage of selegiline (10 mg/day) for the adjunctive treatment of Parkinson's disease (1.75 vs 1.67; n = 13).[18]
- The effect of selegiline transdermal system on pressor sensitivity to tyramine was dose-dependent; after 33 days' treatment, the mean TSF was ≈4-fold higher with 12 mg/24 hours than with 6 mg/24 hours (10.99 vs 2.85, $p < 0.005$; n = 11 vs 12), based on a retrospective comparison of these dosages. However, the increase in tyramine sensitivity with selegiline transdermal system 12 mg/24 hours (the maximum recommended dosage [section 5]) was not exacerbated with longer treatment; the TSF was 9.32 after 93 days' treatment ($p > 0.05$ vs 33 days).[18]
- Moreover, in eight subjects, the mean TSF after 93 days' treatment with selegiline transdermal system 12 mg/24 hours (11.01; measured in the fasting state) was significantly reduced (to 4.46; $p < 0.005$) when these individuals were subsequently re-challenged with tyramine in the fed state, i.e. during a meal.[18]

Other Drug Interaction Studies

- In other drug interactions studies, the pharmacokinetics of selegiline (and/or those of the other agent) were unaltered during coadministration of selegiline transdermal system 6 mg/24 hours with single or multiple doses of alcohol, alprazolam, ibuprofen, ketoconazole, levothyroxine, olanzapine, risperidone or warfarin.[12]
- Concomitant administration of selegiline transdermal system 6 mg/24 hours for 9 or 10 days with pseudoephedrine (60mg three-times daily) or phenylpropanolamine (25mg six-times daily) had no effect on the pharmacokinetics of either of these sympathomimetic agents.[12] There were no clinically relevant changes in blood pressure during coadministration of the selegiline transdermal system with pseudoephedrine or administration of pseudoephedrine alone. In contrast, the incidence of significant blood pressure elevations was higher during coadministration of the selegiline transdermal system and phenylpropanolamine compared with administration of phenylpropanolamine alone (statistical analysis not reported); this is suggestive of a possible pharmacodynamic interaction.[12] It is prudent to avoid concomitant use of a sympathomimetic agent with selegiline transdermal system.[12]
- Carbamazepine is contraindicated with MAO inhibitors, including the selegiline transdermal system[12] (section 5). Approximately 2-fold increases in plasma selegiline concentrations (with variability among subjects) were seen after a single dose of selegiline transdermal system 6 mg/24 hours in patients receiving carbamazepine 400 mg/day for 14 days. The clinical significance of this interaction is unknown.[12]

3. Therapeutic Efficacy

The efficacy of the selegiline transdermal system in the acute or maintenance treatment of MDD has been evaluated in several double-blind, placebo-controlled, multicentre studies (n = 177–322 randomised patients).[19-22]

Adult outpatients (i.e. men and women aged ≥18 years) who had a primary diagnosis of MDD (single or recurrent episode[19-22]), as defined by Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) criteria, were enrolled in these studies.[19-22] Exclusion criteria included: a primary DSM-IV Axis I or Axis II diagnosis other than MDD;[19-22] history of manic or hypomanic episode[19,20,22] (unless clearly secondary to antidepressant therapy[19]); history of psychosis;[20,22] history of substance abuse within previous 6 months;[19,20,22] previous participation in a selegiline transdermal system clinical trial;[22] failure to respond to previous MAO inhibitor treatment;[21,22] failure to re-

spond to more than one adequate trial of an antidepressant for the current episode;[19] and exposure to ECT within the previous 90 days.[19,22]

Patients were required to be free of any psychoactive medications for five pharmacokinetic elimination half-lives[19-22] (at least[21]) or longer if indicated for specific agents[22] (or for 2 weeks, whichever was longer[19,20]). Prior use of MAO inhibitors was not permitted within 2 months of study onset.[19,20] Concomitant use of medications known to interact adversely with MAO inhibitors (e.g. sympathomimetics, SSRIs) was prohibited.[19-22] However, patients followed a tyramine-restricted diet in one study only.[19]

In three short-term studies of 6[19] or 8[20,21] weeks' duration, patients were randomised to fixed doses of selegiline transdermal system 6 mg/24 hours[19,20] or a flexible dose of selegiline transdermal system 6–12 mg/24 hours[21] titrated over 5 weeks (depending on response). Patients in the two selegiline transdermal system 6 mg/24 hours fixed-dose studies[19,20] were required to have a score of ≥20 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17); those whose scores fell below 20 or decreased by ≥20% during a 1-week placebo run-in period ('placebo responders') were excluded. Patients in the flexible-dose study[21] were required to have a HAM-D-17 score of ≥20 and a Clinical Global Impression (CGI)-severity of illness (CGI-S) rating of ≥4 (moderately ill or worse) during screening and baseline visits.

Patients in a long-term relapse-prevention trial[22] were required to have a HAM-D-17 score of ≥18 prior to an initial 10-week, open-label, response-induction phase with selegiline transdermal system 6 mg/24 hours; those who met the criteria for response (HAM-D-17 score of ≤10 during the final 2 weeks of the induction phase) were randomised to 52 weeks' double-blind therapy with selegiline transdermal system 6 mg/24 hours or placebo, without dietary tyramine restrictions.

Efficacy measures in the acute treatment studies included changes from baseline in HAM-D-17, 28-item HAM-D (HAM-D-28) and Montgomery-Asberg Depression Rating Scale (MADRS) scores, and changes in the distribution of CGI-S and CGI-improvement (CGI-I) or -change (CGI-C) ratings.[19-21] Where stated, the mean change in HAM-D-28 score was the primary efficacy endpoint.[21] Patients were defined as responders based on the following criteria (at study endpoint): ≥50% reduction from baseline in HAM-D-17,[19] HAM-D-28[19] or MADRS[20] scores; HAM-D-17 score of <8 (remission);[19] and CGI-I rating of 2 (much improved) or 1 (very much improved).[19]

Relapse, the primary outcome measure in the 1-year study of maintenance therapy, was defined as meeting the following criteria on two consecutive study visits: HAM-D-17 score of ≥14, CGI-S rating of ≥3 (mildly ill or worse, with a ≥2-point increase from double-blind baseline), and DSM-IV criteria for MDD.[22]

Efficacy analyses were performed on the modified intent-to-treat population (i.e. all patients who received double-blind therapy and had ≥1 one post-baseline evaluation)[19-22] using – in the acute treatment studies only[19-21] – the last observation carried forward method.

Acute Treatment

- A fixed dose of selegiline transdermal system 6 mg/24 hours was superior to placebo on almost all efficacy measures in a 6-week pivotal trial in which patients followed a tyramine-restricted diet,[19] and superior to placebo on some outcome measures in another 8-week trial in which patients did not follow a tyramine-restricted diet.[20] Similarly, flexible dosing with selegiline transdermal system 6–12 mg/24 hours was superior to placebo on most efficacy measures in a pivotal 8-week trial conducted without tyramine dietary restrictions.[21]
- In the 6-week, fixed-dose trial of selegiline transdermal system 6 mg/24 hours,[19] the mean HAM-D-17, HAM-D-28 and MADRS scores at baseline were 22.86, 29.69 and 28.85 in the selegiline transdermal system 6 mg/24 hours group (n = 88) and 23.30, 30.78 and 29.53 in the placebo group (n = 88). The mean reductions from baseline (i.e. improvements) in the HAM-D-17, HAM-D-28 and MADRS scores at week 6 were significantly greater

in the selegiline transdermal system group than in the placebo group (8.73 vs 6.10 points [38% vs 26%; p = 0.01], 11.23 vs 7.59 points [38% vs 25%; p = 0.004] and 9.77 vs 5.69 points [34% vs 19%; p = 0.005], respectively).

- Selegiline transdermal system 6 mg/24 hours was superior to placebo on these efficacy measures as early as the first week of treatment.[19]
- At 6 weeks, the improvement in item 1 (depressed mood; −36% vs −26% [p = 0.03]), but not item 3 (suicide; −45% vs −29%), of the HAM-D was significantly greater in the selegiline transdermal system 6 mg/24 hours group than in the placebo group.[19] Additionally, changes in the distribution of CGI-S and CGI-I ratings showed significantly less severity of illness (p = 0.02) and significantly greater global improvement (p = 0.007) in the selegiline transdermal system group than in the placebo group.[19]
- The percentage of responders at week 6 in the selegiline transdermal system 6 mg/24 hours group was significantly higher than that in the placebo group according to all criteria: ≥50% reduction in HAM-D-17 score (38% vs 23%; p = 0.04); ≥50% reduction in HAM-D-28 score (38% vs 23%; p = 0.03); HAM-D-17 score <8 (23% vs 11%; p = 0.04); and CGI-I rating of much improved or very much improved (42% vs 27%; p = 0.03).[19]
- In the 8-week, fixed-dose trial of selegiline transdermal system 6 mg/24 hr,[20] the mean HAM-D-17, HAM-D-28 and MADRS scores at baseline were 22.79, 28.95 and 28.26 in the selegiline transdermal system 6 mg/24 hours group (n = 145) and 22.99, 29.79 and 28.47 in the placebo group (n = 144). Improvements in the HAM-D-28 score (−36% vs −29%; p = 0.039) and MADRS score (−36% vs −24%; p = 0.001) at 8 weeks were significantly greater in the selegiline transdermal system 6 mg/24 hours group (n = 145) than in the placebo group (n = 144), as was the improvement in item 3 of the HAM-D (patients with score of 0 at endpoint: 68% vs 61%; p = 0.021) and the percentage of responders, based on a ≥50% reduction in MADRS score (33% vs 21%; p = 0.031).[20] However, there was no significant between-group difference for the improvement in HAM-D-17 score or the improvement in item 1 of the HAM-D.
- In the flexible-dose trial,[21] the mean HAM-D-28 score at baseline was 28.3 and 28.6 in the selegiline transdermal system 6–12 mg/24 hours and placebo groups, respectively (n = 129 and 128). The improvement in this primary outcome measure was significantly greater in the selegiline transdermal system group than in the placebo group as early as the fifth week of treatment (−9.2 vs −7.1 points [−33% vs −25%; p = 0.03]) and continued through week 8 (−11.1 vs −8.9 points [−39% vs −31%; p = 0.03]).
- Similarly, flexible dosing with selegiline transdermal system 6–12 mg/24 hours produced significantly greater improvements than placebo on the MADRS score after 5 (−31% vs −22%, p = 0.02) and 8 (−40% vs −29%; p = 0.02) weeks, the patient-completed Inventory for Depressive Symptoms, Self-Rated measure after 8 weeks (−37% vs −28%; p = 0.03) and the 6-item HAM-D Bech subscale (depressed mood, feelings of guilt, work and activities, retardation, psychic anxiety and general somatic symptoms) after 5 (−35% vs −25%; p < 0.01) and 8 (−44% vs −33%; p < 0.01) weeks.[21] The end-of-treatment improvement in item 1 of the HAM-D (p < 0.01) was significantly greater in the selegiline transdermal system group than in the placebo group, as was the end-of-treatment improvement in the distribution of CGI-C ratings (p = 0.04).[21]

Maintenance Treatment

- A fixed dose of selegiline transdermal system 6 mg/24 hours was superior to placebo on all outcome measures in the 52-week, pivotal, relapse-prevention trial, which was conducted without tyramine dietary restrictions.[22] Significantly fewer patients randomised to selegiline transdermal system compared with those randomised to placebo met the criteria for relapse at 6 months (17% [n = 149] vs 29% [n = 163]; p = 0.0051) and 1 year (17% [n = 149] vs 31% [n = 163]; p = 0.003).[22]
- Likewise, the Kaplan-Meier estimate of the cumulative rate of relapse/recurrence in the selegiline transdermal system group was significantly lower

than that in the placebo group, both at 6 months ($p = 0.0115$) and at 1 year ($p = 0.0061$).[22] The time to relapse was significantly longer in the selegiline transdermal system group than in the placebo group ($p = 0.0048$).[22]

4. Tolerability

The following tolerability/adverse event profile of the selegiline transdermal system is based almost entirely on the US manufacturer's prescribing information.[12] The premarketing development programme for the selegiline transdermal system included 2036 selegiline exposures in patients with MDD who participated in controlled and uncontrolled clinical trials of the drug. In addition, 702 healthy subjects were exposed to the selegiline transdermal system in clinical pharmacology studies.[12]

- Application site reactions (ASRs; 24%), headache (18%), insomnia (12%), diarrhoea (9%) and dry mouth (8%) were the five most frequent treatment-emergent adverse events among 817 patients with MDD who received the selegiline transdermal system in dosages ranging from 3 to 12 mg/24 hours in short-term placebo-controlled trials of ≤8 weeks' duration.[12]
- According to this pooled analysis,[12] ASRs, which were mostly mild or moderate in severity, were the only adverse events to meet the dual criteria of (i) affecting ≥5% of selegiline transdermal system-treated patients and (ii) occurring at a rate twice that in placebo-treated patients. This was not the case, however, in the short-term, flexible-dose trial,[21] in which four different adverse events satisfied both criteria: ASRs (selegiline transdermal system 6–12 mg/24 hours, 40% [n = 132] vs placebo, 20% [n = 133]); insomnia (30% vs 14%); diarrhoea (10% vs 4%); and pharyngitis (6% vs 2%).
- The pooled discontinuation rate due to adverse events in selegiline transdermal system recipients was approximately twice that in placebo recipients (7.1% [n = 817] vs 3.6% [n = 668]).[12] Withdrawals due to ASRs occurred in 2% of selegiline transdermal system-treated patients compared with 0% of placebo-treated patients.[12]
- The short-term and long-term adverse event profiles of the selegiline transdermal system were qualitatively similar. Thus, the discontinuation rate, due to adverse events with selegiline transdermal system 6 mg/24 hours in the 52-week relapse-prevention trial[22] (section 3), was approximately double that in the placebo group (13.2% [n = 159] vs 6.7% [n = 163]). Of note, ASRs were the only adverse events to satisfy the afore-mentioned dual criteria (15.2% [n = 158] vs 3.7% [n = 163]).
- There have been no reports of hypertensive crisis with the selegiline transdermal system therapy in clinical trials.[12]
- In the pooled analysis of short-term placebo-controlled trials,[12] 3.0% of selegiline transdermal system-treated patients and 1.5% of placebo-treated patients experienced a low systolic blood pressure reading (i.e. ≤90mm Hg, with a ≥20mm Hg change from baseline), while 9.8% of selegiline transdermal system recipients and 6.7% of placebo recipients experienced orthostatic hypotension (i.e. ≥10mm Hg decrease in mean blood pressure with postural change).
- Pooled analyses of placebo-controlled trials revealed no clinically important changes in laboratory test or ECG parameters associated with selegiline transdermal system therapy.[12]
- The selegiline transdermal system and placebo were associated with similar rates of sexual symptoms affecting men (abnormal ejaculation, decreased libido, impotence, anorgasmia; ≤1.0% [n = 304] vs ≤0.4% [n = 256]) or women (decreased libido; 0.0% [n = 513] vs 0.2% [n = 412]) according to a pooled analysis of placebo-controlled trials.[12]
- In a pooled analysis of placebo-controlled trials of 6 or 8 weeks' duration, 2.1% of selegiline transdermal system recipients (n = 757) compared with 2.4% of placebo recipients (n = 614) experienced an increase in bodyweight of ≥5%. However, 5% of selegiline transdermal system recipients compared with 2.8% of placebo recipients experienced a ≥5% loss in bodyweight. The mean change in bodyweight among selegiline transdermal system-treated patients in these trials was −0.54kg compared to +0.14kg in placebo-treated patients.[12]

5. Dosage and Administration

The selegiline transdermal system, in common with all other antidepressant medications, is not approved for use in paediatic patients (FDA black box warning).[12]

The recommended starting and target dose of selegiline transdermal system in adults, including the elderly (aged ≥65 years), is 6 mg/24 hours; tyramine dietary modifications are not required at this dose.

The selegiline transdermal system has been studied in a dosage range of 6–12 mg/24 hours; however, the trials were not designed to assess whether higher doses are more effective than the target dose. If a dose increase is indicated, it should occur in a dose increment of 3 mg/24 hours (up to a maximum dose of 12 mg/24 hours) at intervals of no less than 2 weeks. As with all antidepressants, the full antidepressant effect of the selegiline transdermal system may be delayed.[12]

Patients should be advised to avoid tyramine-rich foods and drinks on the first day of treatment with selegiline transdermal system 9 or 12 mg/24 hours, and for 2 weeks following discontinuation of selegiline transdermal system 9 or 12 mg/24 hours or a dose reduction to 6 mg/24 hours.[12] Selegiline transdermal system patches should be applied to dry, intact skin on the upper torso, the upper thigh or the outer surface of the upper arm.[12]

The selegiline transdermal system is contraindicated with oral selegiline, other MAO inhibitors, SSRIs, serotonin-norepinephrine (noradrenaline) reuptake inhibitors, TCAs, mirtazapine, bupropion, hypericum (St John's wort), sympathomimetic amines (e.g. pseudoephidrine, phenylpropanolamine), dextromethorphan, cyclobenzaprine, carbamazepine/oxcarbazepine and certain analgesic agents, such as pethidine (meperidine), tramadol, methadone and propoxyphene.[12] In general, contraindicated medications should be discontinued for a time period equal to 4–5 pharmacokinetic elimination half-lives (≈1 week for most medications [≈5 weeks for fluoxetine]) before initiating treatment with the selegiline transdermal system. After stopping treatment with the selegiline transdermal system, ≥2 weeks should elapse before starting a contraindicated medication.[12]

Local prescribing information should be consulted for full details of contraindications, warnings and precautions regarding the use of the selegiline transdermal system.

6. Selegiline Transdermal System: Current Status in Major Depressive Disorder

In February 2006, the FDA approved the selegiline transdermal system, the first skin patch for use in the treatment of MDD.[23] Available data (as reviewed here and elsewhere[5]) indicate that the selegiline transdermal system, at a dose of 6 mg/24 hours, is effective and generally well tolerated in the treatment of MDD and can be safely administered without tyramine dietary modifications.

Disclosure

During the peer review process, the manufacturers of the agent under review were offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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