SELEGILINE

**Brands**
- EMSAM  
- Eldepryl  
*see index for additional brand names*

**Generic?**
Yes (oral only)

**Class**
- Neuroscience-based Nomenclature: dopamine, serotonin, norepinephrine enzyme inhibitor (DSM-EI)
- Transdermal: tissue selective monoamine oxidase (MAO) inhibitor (MAO-A and MAO-B inhibitor in brain and relatively selective MAO-B inhibitor in gut)
- Oral: selective MAO-B inhibitor

**Commonly Prescribed for**
(bold for FDA approved)
- Major depressive disorder (transdermal)  
- Oral: Parkinson’s disease or symptomatic parkinsonism (adjunctive)  
- Treatment-resistant depression  
- Panic disorder (transdermal)  
- Social anxiety disorder (transdermal)  
- Treatment-resistant anxiety disorders (transdermal)  
- Alzheimer disease and other dementias (oral)

**How the Drug Works**
- Transdermal selegiline (recommended doses): in the brain, irreversibly inhibits both MAO-A and MAO-B from breaking down norepinephrine, serotonin, and dopamine, which presumably boosts noradrenergic, serotonergic, and dopaminergic neurotransmission  
- Transdermal selegiline (recommended doses): in the gut, is a relatively selective irreversible inhibitor of MAO-B (intestine and liver), reducing the chances of dietary interactions with the MAO-A substrate tyramine  
- Oral: at recommended doses, selectively and irreversibly blocks MAO-B, which presumably boosts dopaminergic neurotransmission  
- Oral: above recommended doses, irreversibly blocks both MAO-A and MAO-B from breaking down norepinephrine, serotonin, and dopamine while simultaneously blocking metabolism of tyramine in the gut  
- Thus, high dose oral administration is not tissue selective and is not MAO-A sparing in the gut, and may interact with tyramine-containing foods to cause hypertension

**How Long Until It Works**
- Onset of therapeutic actions in depression with transdermal administration is usually not immediate, but often delayed 2–4 weeks or longer  
- If it is not working for depression within 6–8 weeks, it may require a dosage increase or it may not work at all  
- May continue to work in depression for many years to prevent relapse of symptoms  
- Can enhance the actions of levodopa in Parkinson’s disease within a few weeks of initiating oral dosing  
- Theoretical slowing of functional loss in both Parkinson’s disease and Alzheimer disease is a provocative possibility under investigation and would take many months or more than a year to observe

**If It Works**
- The goal of treatment in depression is complete remission of current symptoms as well as prevention of future relapses  
- Treatment of depression most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped  
- Continue treatment of depression until all symptoms of depression are gone (remission)  
- Once symptoms of depression are gone, continue treating for 1 year for the first episode of depression  
- For second and subsequent episodes of depression, treatment may need to be indefinite  
- Continue use in Parkinson’s disease as long as there is evidence that selegiline is favorably enhancing the actions of levodopa  
- Use of selegiline to slow functional loss in Parkinson’s disease or Alzheimer disease would be long-term if proven effective for this use

**If It Doesn’t Work**
- Many depressed patients have only a partial response where some symptoms
are improved but others persist (especially insomnia, fatigue, and problems concentrating)
• Other depressed patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
• Some depressed patients who have an initial response may relapse even though they continue treatment, sometimes called “poop out”
• For depression, consider increasing dose, switching to another agent or adding an appropriate augmenting agent, psychotherapy, and evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
• Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and a switch to a mood stabilizer
• Use alternate treatments for Parkinson’s disease or Alzheimer disease

Best Augmenting Combos for Partial Response or Treatment Resistance

✽ Augmentation of selegiline has not been systematically studied in depression, and this is something for the expert, to be done with caution and with careful monitoring
• A stimulant such as d-amphetamine or methylphenidate (with caution and by experts only as use of stimulants with selegiline is listed as a warning; may activate bipolar disorder and suicidal ideation; may elevate blood pressure)
• Lithium
• Mood-stabilizing anticonvulsants
• Atypical antipsychotics (with special caution for those agents with monoamine reuptake blocking properties, such as ziprasidone and zotepine)
• Carbidopa-levodopa (for Parkinson’s disease)

How Drug Causes Side Effects

• At recommended transdermal doses, norepinephrine, serotonin, and dopamine increase in parts of the brain and at receptors other than those that cause therapeutic actions
• At high transdermal doses, loss of tissue selectivity and loss of MAO-A sparing actions in the gut may enhance the possibility of dietary tyramine interactions if MAO-B inhibition occurs in the gut
• At recommended oral doses, dopamine increases in parts of the brain and body and at receptors other than those that cause therapeutic actions
• Side effects are generally immediate, but immediate side effects often disappear in time

Notable Side Effects

• Transdermal: application site reactions, headache, insomnia, diarrhea, dry mouth
• Oral: exacerbation of levodopa side effects, especially nausea, dizziness, abdominal pain, dry mouth, headache, dyskinesia, confusion, hallucinations, vivid dreams
Many side effects cannot be improved with an augmenting agent, especially at lower doses.

**Life-Threatening or Dangerous Side Effects**
- Transdermal: hypertensive crisis was not observed with preliminary experience in clinical trials, even in patients who were not following a low tyramine diet
- Oral: hypertensive crisis (especially when MAOIs are used with certain tyramine-containing foods or prohibited drugs) – reduced risk at low oral doses compared to nonselective MAOIs
- Theoretically, when used at high doses may induce seizures and mania as do nonselective MAOIs
- Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

**Weight Gain**
- Transdermal: reported but not expected; some patients may experience weight loss
- Oral: occurs in significant minority

**Sedation**
- Reported but not expected
- Can be activating in some patients

**What to Do About Side Effects**
- Wait
- Wait
- Wait
- Lower the dose
- Switch after appropriate washout to an SSRI or newer antidepressant (depression)
- Switch to other antiparkinsonian therapies (Parkinson’s disease)

**Best Augmenting Agents for Side Effects**
- Trazodone (with caution) for insomnia in depression
- Benzodiazepines for insomnia in depression
- Single oral or sublingual dose of a calcium channel blocker (e.g., nifedipine) for urgent treatment of hypertension due to drug interaction or dietary tyramine

**DOSING AND USE**

**Usual Dosage Range**
- Depression (transdermal): 6 mg/24 hours–12 mg/24 hours
- Depression (oral): 30–60 mg/day
- Parkinson’s disease/Alzheimer disease: 5–10 mg/day

**Dosage Forms**
- Transdermal patch 20 mg/20 cm² (6 mg/24 hours), 30 mg/30 cm² (9 mg/24 hours), 40 mg/40 cm² (12 mg/24 hours)
- Capsule 5 mg
- Tablet 5 mg scored
- Orally disintegrating tablet 1.25 mg

**How to Dose**
- Depression (transdermal): initial 6 mg/24 hours; can increase by 3 mg/24 hours every 2 weeks; maximum dose generally 12 mg/24 hours
- Parkinson’s disease: initial 2.5 mg/day twice daily; increase to 5 mg twice daily; reduce dose of levodopa after 2–3 days

**Dosing Tips**
- Transdermal patch contains 1 mg of selegiline per 1 cm² and delivers approximately 0.3 mg of selegiline per cm² over 24 hours
- Patch is available in three sizes – 20 mg/20 cm², 30 mg/30 cm², and 40 mg/40 cm² – that deliver doses of approximately 6 mg, 9 mg, and 12 mg, respectively, over 24 hours
- At 6 mg/24 hours (transdermal) dietary adjustments are not generally required
- Dietary modifications to restrict tyramine intake from foods are recommended for doses above 6 mg/24 hours (transdermal)
- Transdermal patch should only be applied to dry, intact skin on the upper torso, upper thigh, or outer surface of the upper arm
- New application site should be selected for each day; patch should be applied at approximately the same time every day; only one patch should be applied at a time; patches should not be cut.
SELEGILINE (continued)

- Avoid touching the exposed (sticky) side of the patch, and after application, wash hands with soap and water; do not touch eyes until after hands have been washed
- Heat could theoretically increase the amount of selegiline absorbed from the transdermal patch, so patients should avoid exposing the application site to external sources of direct heat (e.g., heating pads, prolonged direct sunlight)
- Although there is theoretically a 3-day reservoir of drug in each patch, multiday administration from a single patch is generally not recommended and has not been tested; because of residual drug in the patch after 24 hours of administration, discard used patches in a manner that prevents accidental application or ingestion by children, pets, or others
- For Parkinson's disease, oral dosage above 10 mg/day generally not recommended
- Dosage of carbidopa-levodopa can at times be reduced by 10–30% after 2–3 days of administering oral selegiline 5–10 mg/day in Parkinson's disease
- At doses above 10 mg/day (oral), selegiline may become nonselective and inhibit both MAO-A and MAO-B
- At doses above 30 mg/day (oral), selegiline may have antidepressant properties
- Patients receiving high oral doses may need to be evaluated periodically for effects on the liver
- Doses above 10 mg/day (oral) may increase the risk of hypertensive crisis, tyramine interactions, and drug interactions similar to those of phenelzine and tranylcypromine

Overdose
- Overdose with the transdermal formulation is likely to produce substantial amounts of MAO-A inhibition as well as MAO-B inhibition, and should be treated the same as overdose with a nonselective oral MAOI
- Dizziness, anxiety, ataxia, insomnia, sedation, irritability, headache; cardiovascular effects, confusion, respiratory depression, coma

Drug Interactions
- Many misunderstandings about what drugs can be combined with MAOIs
- Theoretically and especially at high doses, selegiline could cause a fatal “serotonin syndrome” when combined with drugs that block serotonin reuptake, so do not use with a serotonin reuptake inhibitor for up to 5 half-lives after stopping the serotonin reuptake inhibitor (i.e., “wash-in” of selegiline should be about 1 week after discontinuing most agents [except 5 weeks or more after discontinuing fluoxetine because of its long half-life and that of its active metabolite]) (see Table 1 after Pearls)

Habit Forming
- Lack of evidence for abuse potential with transdermal selegiline despite its metabolism to l-amphetamine and l-methamphetamine
- Some patients have developed dependence to other MAOIs

How to Stop
- Transdermal: MAOI slowly recovers over 2–3 weeks after patch removed
- Oral: generally no need to taper, as the drug wears off slowly over 2–3 weeks

Pharmacokinetics
- Clinical duration of action may be up to 14 days due to irreversible enzyme inhibition
- Major metabolite of selegiline is desmethylselegiline; other metabolites are l-methamphetamine and l-amphetamine
- Because first-pass metabolism is not extensive with transdermal dosing, this results in notably higher exposure to selegiline and lower exposure to metabolites as compared to oral dosing
- With transdermal selegiline, 25–30% of selegiline content is delivered systemically over 24 hours from each patch
- Mean half-life of transdermal selegiline is approximately 18–25 hours
- Steady-state mean elimination half-life of oral selegiline is approximately 10 hours

Long-Term Use
- Long-term use has not been systematically studied although generally recommended for chronic use as for other antidepressants

Avoid touching the exposed (sticky) side of the patch, and after application, wash hands with soap and water; do not touch eyes until after hands have been washed.
SELEGILINE

be comparable to that of low-dose oral selegiline (10 mg) with neither causing a hypertensive reaction to high tyramine meals

• Tyramine sensitivity and hypertensive responses to the high-dose transdermal patch (12 mg/24 hours) may occur with administration of 70–100 mg of tyramine in the fasted state, so dietary restrictions may also not be necessary at 9 mg/24 hours or 12 mg/24 hours of transdermal administration of selegiline

• However, insufficient studies have been performed to be sure of the safety of transdermal administration at 9 mg/24 hours or 12 mg/24 hours, so dietary restrictions of tyramine are still recommended at these higher doses

• Oral administration of nonselective irreversible MAOIs generally requires adherence to a low tyramine diet (see Table 2 after Pearls)

• Ingestion of a “high tyramine meal” defined as 40 mg or more of tyramine in the fasted state or as little as ingestion of 10 mg of tyramine in the fasted state can cause hypertensive reactions in patients taking a nonselective irreversible MAOI orally

• Food restrictions (see Table 2 after Pearls) are generally recommended for patients taking the higher doses of transdermal selegiline (9 mg/24 hours or 12 mg/24 hours) but not for the lower doses of transdermal selegiline (6 mg/24 hours) or for the low dose orally (10 mg)

• Transdermal: studies of low-dose transdermal administration of selegiline (6 mg/24 hours) failed to show changes in systolic or diastolic blood pressure or pulse when administered to normal volunteers taking either pseudoephedrine 60 mg three times a day for 2 days or 25 mg of phenylpropanolamine (no longer commercially available in the USA) every 4 hours for 1 day

• However, sufficient safety information is not available to recommend administration of pseudoephedrine without a precaution; blood pressure should be monitored if low-dose transdermal selegiline is given at all with pseudoephedrine

• Pseudoephedrine may need to be avoided when administering transdermal selegiline,
SELEGILINE (continued)

particularly at higher doses of selegiline or in vulnerable patients with hypertension

- Although risk may be reduced with transdermal administration of selegiline, patient and prescriber must be vigilant to potential interactions with any drug, including antihypertensives and over-the-counter cough/cold preparations
- Over-the-counter medications to avoid or use with caution under the care of an expert include cough and cold preparations, including those containing dextromethorphan, nasal decongestants (tablets, drops, or spray), hay-fever medications, sinus medications, asthma inhalant medications, anti-appetite medications, weight reducing preparations, “pep” pills (see Table 3 after Pearls)
- Certain transdermal patches containing even small traces of aluminum or other metals in the adhesive backing can cause skin burns if worn during MRI, so warn patients taking the transdermal formulation about this possibility and advise them to disclose this information if they need an MRI
- Hypoglycemia may occur in diabetic patients receiving insulin or oral antidiabetic agents
- Use cautiously in patients receiving reserpine, anesthetics, disulfiram, metrizamide, anticholinergic agents
- Selegiline is not recommended for use in patients who cannot be monitored closely
- Only use sympathomimetic agents or guanethidine with oral doses of selegiline below 10 mg/day
- When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
- Distribute the brochures provided by the FDA and the drug companies
-Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
- Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use

- If patient is taking meperidine (pethidine)
- If patient is taking a sympathomimetic agent or taking guanethidine
- If patient is taking another MAOI
- If patient is taking any agent that can inhibit serotonin reuptake (e.g., SSRIs, sibutramine, tramadol, milnacipran, duloxetine, venlafaxine, clomipramine, etc.)
- If patient is taking diuretics, dextromethorphan
- If patient is taking St. John’s wort, cyclobenzaprine, methadone, propoxyphene
- If patient has phaeochromocytoma
- If patient is undergoing elective surgery and requires general anesthesia
- If there is a proven allergy to selegiline

SPECIAL POPULATIONS

Renal Impairment
- No dose adjustment necessary for transdermal administration in patients with mild to moderate renal impairment
- Use oral administration with caution – drug may accumulate in plasma in patients with renal impairment
- Oral administration may require lower than usual adult dose

Hepatic Impairment
- No dose adjustment necessary for transdermal administration in patients with mild to moderate hepatic impairment
- Oral administration may require lower than usual adult dose

Cardiac Impairment
- May require lower than usual adult dose
- Observe closely for orthostatic hypotension

Elderly
- Recommended dose for patients over 65 years old is 20 mg oral and 6 mg/day transdermal
- Dose increases in the elderly should be made with caution and patients should be observed for postural changes in blood pressure throughout treatment
- Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older
**Children and Adolescents**
- Not recommended for use in children under 18
- Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients
- Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
- Monitor patients face-to-face regularly, particularly during the first several weeks of treatment

**Pregnancy**
- Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

**Breast Feeding**
- Some drug is found in mother’s breast milk
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be reinstituted late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Should evaluate patient for treatment with an antidepressant with a better risk/benefit ratio

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**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**
- Treatment-resistant depression
- Patients with atypical depression (hypersomnia, hyperphagia)
- Patients who wish to avoid weight gain and sexual dysfunction
- Parkinson’s patients inadequately responsive to levodopa

**Potential Disadvantages**
- Noncompliant patients
- Patients with motor complications and fluctuations on levodopa treatment
- Patients with cardiac problems or hypertension

**Primary Target Symptoms**
- Depressed mood (depression)
- Somatic symptoms (depression)
- Sleep and eating disturbances (depression)
- Psychomotor disturbances (depression)
- Motor symptoms (Parkinson’s disease)

**Pearls**
- Transdermal administration may allow freedom from dietary restrictions
- Transdermal selegiline theoretically appealing as a triple action agent (serotonin, norepinephrine, and dopamine) for treatment-refractory and difficult cases of depression
- Transdermal selegiline may have low risk of weight gain and sexual dysfunction, and may be useful for cognitive dysfunction in attention deficit disorder and other cognitive disorders, as it increases dopamine and is metabolized to l-amphetamine and l-methamphetamine
- Low-dose oral administration generally used as an adjunctive treatment for Parkinson’s disease after other drugs have lost efficacy
- At oral doses used for Parkinson’s disease, virtually no risk of interactions with food
- Neuroprotective effects are possible but unproved
- Enhancement of levodopa action can occur for Parkinson’s patients at low oral doses, but antidepressant actions probably require high oral doses that do not have the potential tissue selectivity and lack
of dietary restrictions of the low-dose transdermal formulation

- High doses may lose safety features
- MAOIs are generally reserved for second-line use after SSRIs, SNRIs, and combinations of newer antidepressants have failed
- Patient should be advised not to take any prescription or over-the-counter drugs without consulting their doctor because of possible drug interactions
- Headache is often the first symptom of hypertensive crisis

- Myths about the danger of dietary tyramine can be exaggerated, but prohibitions against concomitant drugs often not followed closely enough
- Combining multiple psychotropic agents with MAOIs should be for the expert, especially if combining with agents of potential risk (e.g., stimulants, trazodone, TCAs)
- MAOIs should not be neglected as therapeutic agents for the treatment-resistant

Table 1. Drugs contraindicated due to risk of serotonin syndrome/toxicity

<table>
<thead>
<tr>
<th>Do Not Use:</th>
<th>Drugs of Abuse</th>
<th>Opioids</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Drugs of Abuse</td>
<td>Opioids</td>
<td>Other</td>
</tr>
<tr>
<td>SSRI</td>
<td>MDMA (ecstasy)</td>
<td>Meperidine</td>
<td>Non-subcutaneous sumatriptan</td>
</tr>
<tr>
<td>SNRI</td>
<td>Cocaine</td>
<td>Tramadol</td>
<td>Chlorpheniramine</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Methamphetamine</td>
<td>Methadone</td>
<td>Brompheniramine</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>High-dose or injected amphetamine</td>
<td>Fentanyl</td>
<td>Dextromethorphan</td>
</tr>
</tbody>
</table>

Table 2. Dietary guidelines for patients taking MAOIs

<table>
<thead>
<tr>
<th>Foods to avoid*</th>
<th>Foods allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried, aged, smoked, fermented, spoiled, or improperly stored meat, poultry, and fish</td>
<td>Fresh or processed meat, poultry, and fish; properly stored pickled or smoked fish</td>
</tr>
<tr>
<td>Broad bean pods</td>
<td>All other vegetables</td>
</tr>
<tr>
<td>Aged cheeses</td>
<td>Processed cheese slices, cottage cheese, ricotta cheese, yogurt, cream cheese</td>
</tr>
<tr>
<td>Tap and unpasteurized beer</td>
<td>Canned or bottled beer and alcohol</td>
</tr>
<tr>
<td>Marmite</td>
<td>Brewer’s and baker’s yeast</td>
</tr>
<tr>
<td>Sauerkraut, kimchee</td>
<td></td>
</tr>
<tr>
<td>Soy products/soybean</td>
<td>Peanuts</td>
</tr>
<tr>
<td>Banana peel</td>
<td>Bananas, avocados, raspberries</td>
</tr>
<tr>
<td>Tyramine-containing nutritional supplement</td>
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</tbody>
</table>

*Not necessary for 6-mg transdermal or low-dose oral selegiline
Table 3. Drugs that boost norepinephrine: should only be used with caution with MAOIs

<table>
<thead>
<tr>
<th>Use With Caution:</th>
<th>Decongestants</th>
<th>Stimulants</th>
<th>Antidepressants with norepinephrine reuptake inhibition</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine</td>
<td>Amphetamines</td>
<td>Most tricyclics</td>
<td>Phentermine</td>
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<tr>
<td>Pseudoephedrine</td>
<td>Methylphenidate</td>
<td>NRI's</td>
<td></td>
<td>Local anesthetics containing vasoconstrictors</td>
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<tr>
<td>Cocaine</td>
<td></td>
<td>NDRI's</td>
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<td>Methamphetamine</td>
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<tr>
<td>Modafinil</td>
<td></td>
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<td>Tapentadol</td>
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<tr>
<td>Armodafinil</td>
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Suggested Reading

