Selegiline transdermal patch (EMSAM®)

Somerset Pharmaceuticals, Inc. (a joint venture of Mylan Laboratories Inc. and Watson Pharmaceuticals, Inc.) and Bristol-Myers Squibb Company (commercialization and distribution)

Acute and maintenance treatment of patients with major depressive disorder (MDD)

On January 31, 2004, the US Food and Drug Administration (FDA) issued an “Approvable” letter to Somerset for EMSAM® (20 mg, 30 mg, and 40 mg).

Selegiline is a monoamine oxidase inhibitor (MAOI). It is available in tablet form to treat Parkinson’s disease. EMSAM® delivers a constant dose of selegiline through the skin.

There are two types of MAO isoenzymes: MAO-A and MAO-B. MAO-A is the predominant form in the digestive tract, and MAO-B is predominant in the central nervous system (CNS).

In the CNS, MAO helps control the concentration of dopamine, serotonin, and norepinephrine. MAOIs, including selegiline, inhibit the breakdown of these neurotransmitters. This inhibition increases the concentrations of neurotransmitters in the brain, and may ease depressive symptoms.

In the digestive tract, MAO protects against the hypertensive effects of dietary tyramine, a compound that is commonly found in aged cheese, red wine, and chocolate. At doses required to achieve antidepressant efficacy (i.e., 30 mg to 60 mg), selegiline interferes with the breakdown of tyramine, which may result in dangerous and sudden increases in blood pressure. EMSAM® bypasses the gastrointestinal system, permitting adequate brain MAO inhibition, while maintaining the integrity of the gastrointestinal barrier to ingested tyramine.

MDD is characterized by at least two weeks of depressed mood, or loss of interest or pleasure in nearly all activities. These and other symptoms cause substantial distress or functional impairment. Treatment approaches include pharmacotherapy and psychotherapy. Antidepressant medications include tricyclic agents (e.g., amitriptyline), selective serotonin reuptake inhibitors (e.g., citalopram, fluoxetine, paroxetine, and sertraline), and atypical antidepressants (e.g., bupropion, nefazodone, and venlafaxine). Oral MAO inhibitors such as phenelzine are also used but with dietary restrictions. Psychotherapy interventions include cognitive-behavioural therapy, interpersonal therapy, and problem-solving therapy. Electroconvulsive therapy is generally reserved for patients with severe, unmanageable MDD.
Emerging Drug List
SELEGILINE TRANSDERMAL PATCH

Cost: There is no costing information for EMSAM®, as it is not currently marketed in any country.

Evidence: The efficacy and safety of EMSAM® has been demonstrated in two randomized, double-blind, placebo-controlled studies of six and eight weeks’ duration in adult outpatients (18 years to 70 years of age) meeting DSM-IV criteria for MDD. In both studies, patients were randomized to receive treatment with EMSAM® (20 mg/20 cm²) or placebo. Treatment was preceded by a one-week, single-blind, placebo run-in period to identify and eliminate placebo responders. In the six-week study, 177 patients followed a tyramine-restricted diet during treatment, and for two weeks after the study. At six weeks, EMSAM®-treated patients demonstrated significant improvements on the 17-item (p=0.01) and 28-item (p=0.004) Hamilton Depression Scale (HAM-D), but not on the item assessing suicide. A significant improvement over placebo was also observed on the Clinical Global Impression scale (CGI, p=0.007) and the Montgomery-Asberg Depression Rating Scale (MADRS, p=0.005). In the eight-week study, 289 patients were not subjected to dietary tryamine restrictions. At eight weeks, EMSAM®-treated patients showed a significant improvement compared to placebo on MADRS (p=0.001) and HAM-D-28 (p=0.039). No hypertensive effects were observed in either study.

In a longer, unpublished trial, 322 patients with MDD who had responded to 20 mg EMSAM® during an initial 10-week open-label treatment phase were randomized to continue EMSAM® or to take placebo for up to 52 weeks. Patients who continued treatment with EMSAM® experienced a significantly longer time to relapse compared with those receiving placebo (p=0.006). No specific data on the time to relapse were provided.

Based on these trials, the US FDA’s Psychopharmacologic Drugs Advisory Committee concluded (October 2005) that the 20 mg formulation of EMSAM® could be safely administered without tyramine dietary modifications, and that there was insufficient evidence to waive the dietary warning for higher doses.

Adverse Effects: The most common adverse effects are application site reactions, including rash, itching, or irritation, all of which are mild or moderate in severity, and generally do not require further treatment. Weight changes and levels of sexual dysfunction are similar between EMSAM® and placebo-treated patients.

Commentary: EMSAM® offers a better drug interaction and adverse event profile than oral selegiline. If approved, it would be the first transdermal treatment for MDD. The advantages associated with transdermal drug delivery include avoidance of first-pass metabolism and improved patients’ compliance. Limitations include the inability to precisely control the dosage to each patient, and cost, as many oral antidepressants are available in generic
form. Dietary tyramine restrictions for higher EMSAM® doses could lead to confusion for patients who are titrating 20 mg to 30 mg and 40 mg doses, and could discourage some from using EMSAM®. More safety data on higher EMSAM® doses should be gathered, so that the dietary warning can be appropriately interpreted. Studies that compare EMSAM® with conventional antidepressant medications would also be beneficial.

References:


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

These summaries have not been externally peer reviewed.

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