



Dey Pharma Fact Sheet

Dey Pharma ▶ 110 Allen Road ▶ Basking Ridge, N.J. 07920 ▶ www.dey.com

Main Number: 908.542.1999

Government Relations: 724.514.1835, government.relations@mylan.com

Media Relations: 724.514.1968, gpa@mylan.com

OVERVIEW

Dey Pharma is a specialty pharmaceutical company focused on the development, manufacturing and marketing of prescription drug products for the treatment of respiratory diseases, severe allergic reactions and psychiatric disorders. It is a subsidiary of Mylan (Nasdaq: MYL), a Fortune 500 company that ranks among the leading generic and specialty pharmaceuticals companies in the world and provides products to customers in more than 150 countries and territories.

Dey's ability to develop, manufacture and commercialize innovative brand products, combined with Mylan's global footprint, highly efficient operating platform and unrivaled reputation for service, quality and reliability allow the company to help people around the world live healthier lives.

FAST FACTS

- ▶ Founded in 1978
- ▶ Corporate headquarters located in Basking Ridge, N.J., with operations in Napa, Calif. and Allen, Texas
- ▶ Markets products in the U.S. to a variety of customer audiences, including health care practitioners, wholesalers, pharmacists, pharmacy chains, home health and long-term care providers
- ▶ Manufactures nebulized form fill seal products at its Napa facility for U.S. distribution. Products include Perforomist®, DuoNeb®, AccuNeb®, albuterol and ipratropium
- ▶ Approximately 700 employees based in the U.S., with a field-based sales force of approximately 280 individuals
- ▶ Revenues of \$428 million in 2010
- ▶ EpiPen® Auto-Injector is the no. 1 prescribed auto-injector with over 90% market share in the U.S. and worldwide.

PRODUCT PORTFOLIO

EPIPEN 2-PAK® EPIPEN Jr 2-PAK®
(Epinephrine) Auto-Injectors 0.3/0.15mg

Perforomist®
(formoterol fumarate) Inhalation Solution
20 mcg/2 mL vial

EMSAM® 6 mg/24 hr
(selegiline transdermal system)

Please see attached full prescribing and safety information for EpiPen® Auto-Injector.

Please see attached full prescribing information, including Boxed Warning for Perforomist® Inhalation Solution and EMSAM® (selegiline transdermal system).

For more information, please visit:

www.dey.com, www.epipen.com, www.perforomist.com, www.emsam.com and www.mylan.com

Perforomist® is a registered trademark of Dey Pharma, L.P.

EpiPen®, EpiPen® Jr, EpiPen 2-Pak®, and EpiPen Jr 2-Pak® are registered trademarks of Mylan Inc. licensed exclusively to its wholly owned subsidiary, Dey Pharma, L.P. EpiPen Auto-Injectors are manufactured for Dey Pharma, L.P. by Meridian Medical Technologies, Inc.

EMSAM® is a registered trademark of Somerset Pharmaceuticals, Inc. EMSAM (selegiline transdermal system) is manufactured for Somerset Pharmaceuticals, Inc. by Mylan Technologies, Inc., and is distributed by Dey Pharma, L.P.

PRESCRIBING INFORMATION

EPIPEN®

(epinephrine) Auto-Injector 0.3 mg
EpiPen® = one dose of 0.30 mg epinephrine (USP, 1:1000, 0.3 mL)

EPIPEN® JR

(epinephrine) Auto-Injector 0.15 mg
EpiPen® Jr = one dose of 0.15 mg epinephrine (USP, 1:2000, 0.3 mL)



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PRESCRIBING INFORMATION

DESCRIPTION

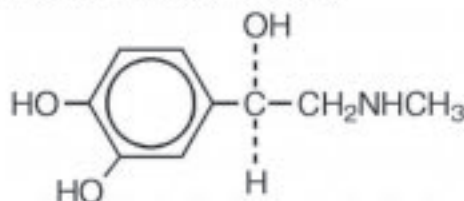
Each EpiPen® Auto-Injector delivers a **single dose** of 0.3 mg epinephrine injection, USP, 1:1000 (0.3 mL) in a sterile solution.

Each EpiPen® Jr Auto-Injector delivers a **single dose** of 0.15 mg epinephrine injection, USP, 1:2000 (0.3 mL) in a sterile solution.

The EpiPen® and EpiPen® Jr Auto-Injectors each contain 2 mL epinephrine solution. Approximately 1.7 mL remains in the auto-injector after activation and cannot be used.

Each 0.3 mL in the EpiPen® Auto-Injector contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.2-5.0. Each 0.3 mL in the EpiPen® Jr Auto-Injector contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and Water for Injection. The pH range is 2.2-5.0.

Epinephrine is a sympathomimetic catecholamine. Chemically, epinephrine is B-(3, 4-dihydroxyphenyl)- α -methylaminoethanol, with the following structure:



Epinephrine solution deteriorates rapidly on exposure to air or light, turning pink from oxidation to adrenochrome and brown from the formation of melanin. Replace EpiPen® and EpiPen® Jr Auto-Injectors if the epinephrine solution appears discolored.

EpiPen® and EpiPen® Jr Auto-Injectors do not contain latex.

CLINICAL PHARMACOLOGY

Epinephrine is the drug of choice for the emergency treatment of severe allergic reactions (Type I) to insect stings or bites, foods, drugs, and other allergens. It can also be used in the treatment of anaphylaxis of unknown cause (idiopathic anaphylaxis) or exercise-induced anaphylaxis. When given intramuscularly or subcutaneously it has a rapid onset and short duration of action. Epinephrine acts on both alpha and beta adrenergic receptors. Through its action on alpha adrenergic receptors, epinephrine lessens the vasodilation and increased vascular permeability that occurs during anaphylaxis, which can lead to loss of intravascular fluid volume and hypotension. Through its action on beta-adrenergic receptors, epinephrine causes bronchial smooth muscle relaxation that helps alleviate bronchospasm, wheezing and dyspnea that may occur during anaphylaxis. Epinephrine also alleviates pruritus, urticaria, and angioedema and may be effective in relieving gastrointestinal and genitourinary symptoms associated with anaphylaxis because of its relaxer effects on the smooth muscle of the stomach, intestine, uterus, and urinary bladder.

INDICATIONS AND USAGE

EpiPen® and EpiPen® Jr Auto-Injectors are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects (e.g., order Hymenoptera, which include bees, wasps, hornets, yellow jackets and fire ants) and biting insects (e.g., triatoma, mosquitos), allergen immunotherapy, foods, drugs, diagnostic testing substances (e.g., radiocontrast media) and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. EpiPen® and EpiPen® Jr Auto-Injectors are intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions. Selection of the appropriate dosage strength is determined according to patient body weight (see **DOSE AND ADMINISTRATION** section).

Such reactions may occur within minutes after exposure and consist of flushing, apprehension, syncope, tachycardia, thready or unobtainable pulse associated with a fall in blood pressure, convulsions, vomiting, diarrhea and abdominal cramps, involuntary voiding, wheezing, dyspnea due to laryngeal spasm, pruritus, rashes, urticaria or angioedema.

EpiPen® and EpiPen® Jr Auto-Injectors are intended for immediate self-administration as emergency supportive therapy only and are not a substitute for immediate medical care.

CONTRAINDICATIONS

There are no absolute contraindications to the use of epinephrine in a life-threatening situation.

WARNINGS

EpiPen® and EpiPen® Jr Auto-Injectors should **only** be injected into the anterolateral aspect of the thigh. **DO NOT INJECT INTO BUTTOCK.** Injection into the buttock may not provide effective treatment of anaphylaxis. Advise the patient to go immediately to the nearest emergency room for further treatment of anaphylaxis.

Since epinephrine is a strong vasoconstrictor, accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area. Treatment should be directed at vasodilation in addition to further treatment of anaphylaxis (see **ADVERSE REACTIONS**). Advise the patient to go immediately to the nearest emergency room and to inform the healthcare provider in the emergency room of the location of the accidental injection.

DO NOT INJECT INTRAVENOUSLY. Large doses or accidental intravenous injection of epinephrine may result in cerebral hemorrhage due to sharp rise in blood pressure. Rapidly acting vasodilators can counteract the marked pressor effects of epinephrine if there is such inadvertent administration.

Epinephrine is the preferred treatment for serious allergic reactions or other emergency situations even though this product contains sodium metabisulfite, a sulfite that may, in other products, cause allergic-type reactions including anaphylactic symptoms or life-threatening or less severe asthmatic episodes in certain susceptible persons. The alternatives to using epinephrine in a life-threatening situation may not be satisfactory. The presence of a sulfite in this product should not deter administration of the drug for treatment of serious allergic or other emergency situations even if the patient is sulfite-sensitive.

Epinephrine should be administered with caution in patients who have heart disease, including patients with cardiac arrhythmias, coronary artery or organic heart disease, or hypertension. In such patients, or in patients who are on drugs that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, or anti-arrhythmics, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias. It should be recognized that the presence of these conditions is not a contraindication to epinephrine administration in an acute, life-threatening situation.

Epinephrine is light sensitive and should be stored in the carrier tube provided. Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) (See USP Controlled Room Temperature). Do not refrigerate. Before using, check to make sure the solution in the auto-injector is not discolored. Replace the auto-injector if the solution is discolored or contains a precipitate.

PRECAUTIONS

(1) General

EpiPen® and EpiPen® Jr Auto-Injectors are not intended as a substitute for immediate medical care. In conjunction with the administration of epinephrine, the patient should seek immediate medical or hospital care. More than two sequential doses of epinephrine should only be administered under direct medical supervision.

Epinephrine is essential for the treatment of anaphylaxis. Patients with a history of severe allergic reactions (anaphylaxis) to insect stings or bites, foods, drugs, and other allergens as well as idiopathic and exercise-induced anaphylaxis should be carefully instructed about the circumstances under which epinephrine should be used. It must be clearly determined that the patient is at risk of future anaphylaxis, since the following risks may be associated with epinephrine administration (see **DOSE AND ADMINISTRATION**).

Epinephrine should be used with caution in patients who have cardiac arrhythmias, coronary artery or organic heart disease, hypertension, or in patients who are on drugs that may sensitize the heart to arrhythmias, e.g., digitalis, diuretics, quinidine, or other anti-arrhythmics. In such patients, epinephrine may precipitate or aggravate angina pectoris as well as produce ventricular arrhythmias.

The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors.

Some patients may be at greater risk of developing adverse reactions after epinephrine administration. These include: hyperthyroid individuals, individuals with cardiovascular disease, hypertension, or diabetes, elderly individuals, pregnant women, pediatric patients under 30 kg (66 lbs.) body weight using EpiPen® Auto-Injector, and pediatric patients under 15 kg (33 lbs.) body weight using EpiPen® Jr Auto-Injector.

Despite these concerns, epinephrine is essential for the treatment of anaphylaxis. Therefore, patients with these conditions, and/or any other person who might be in a position to administer EpiPen® or EpiPen® Jr Auto-Injector to a patient experiencing anaphylaxis should be carefully instructed in regard to the circumstances under which epinephrine should be used.

(2) Information for Patients

Complete patient information, including dosage, direction for proper administration and precautions can be found inside each EpiPen®/EpiPen® Jr Auto-Injector carton.

Epinephrine may produce symptoms and signs that include an increase in heart rate, the sensation of a more forceful heartbeat, palpitations, sweating, nausea and vomiting, difficulty breathing, pallor, dizziness, weakness or shakiness, headache, apprehension, nervousness, or anxiety. These symptoms and signs usually subside rapidly, especially with rest, quiet and recumbency. Patients with hypertension or hyperthyroidism may develop more severe or persistent effects, and patients with coronary artery disease could experience angina. Patients with diabetes may develop increased blood glucose levels following epinephrine administration. Patients with Parkinson's disease may notice a temporary worsening of symptoms.

In case of accidental injection, the patient should be advised to immediately go to the emergency room for treatment. Since the epinephrine in the EpiPen® Auto-Injector is a strong vasoconstrictor when injected into the digits, hands or feet, treatment should be directed at vasodilation if there is such an inadvertent administration to these areas (see **ADVERSE REACTIONS**).

(3) Drug Interactions

Patients who receive epinephrine while concomitantly taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

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The effects of epinephrine may be potentiated by tricyclic anti-depressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines, notably chlorpheniramine, tripelemamine and diphenhydramine.

The cardiostimulating and bronchodilating effects of epinephrine are antagonized by beta-adrenergic blocking drugs, such as propranolol. The vasoconstricting and hypertensive effects of epinephrine are antagonized by alpha-adrenergic blocking drugs, such as phentolamine. Ergot alkaloids may also reverse the pressor effects of epinephrine.

(4) Carcinogenesis, Mutagenesis, Impairment of Fertility

Epinephrine and other catecholamines have been shown to have mutagenic potential *in vitro* and to be an oxidative mutagen in a WP2 bacterial reverse mutation assay. Epinephrine had a moderate degree of mutagenicity, and was positive in the DNA Repair test with *β. subtilis* (REC) assay, but was not mutagenic in the *Salmonella* bacterial reverse mutation assay.

Studies of epinephrine after repeated exposure in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility have not been conducted. This should not prevent the use of epinephrine under the conditions noted under **INDICATIONS AND USAGE**.

(5) Usage in Pregnancy

Pregnancy Category C: There is no study on the acute effect of epinephrine on pregnancy. Epinephrine has been shown to have developmental effects when administered subcutaneously in rabbits at a dose of 1.2 mg/kg daily for two to three days (approximately 30 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m² basis), in mice at a subcutaneous dose of 1 mg/kg daily for 10 days (approximately 7 times the maximum daily subcutaneous or intramuscular dose on a mg/m² basis) and in hamsters at a subcutaneous dose of 0.5 mg/kg daily for 4 days (approximately 5 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m² basis). These effects were not seen in mice at a subcutaneous dose of 0.5 mg/kg daily for 10 days (approximately 3 times the maximum recommended daily subcutaneous or intramuscular dose on a mg/m² basis). Although, there are no adequate and well-controlled studies in pregnant women, epinephrine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS

Adverse reactions to epinephrine include transient, moderate anxiety; apprehensiveness; restlessness; tremor; weakness; dizziness; sweating; palpitations; pallor; nausea and vomiting; headache; and/or respiratory difficulties. These symptoms occur in some persons receiving therapeutic doses of epinephrine, but are more likely to occur in patients with hypertension or hyperthyroidism. Arrhythmias, including fatal ventricular fibrillation, have been reported in patients with underlying cardiac disease or certain drugs (see **PRECAUTIONS, Drug Interactions**). Rapid rises in blood pressure have produced cerebral hemorrhage, particularly in elderly patients with cardiovascular disease. Angina may occur in patients with coronary artery disease. The potential for epinephrine to produce these types of adverse reactions does not contraindicate its use in an acute life-threatening allergic reaction.

Accidental injection into the digits, hands or feet may result in loss of blood flow to the affected area (see **WARNINGS**). Adverse events experienced as a result of accidental injections may include increased heart rate, local reactions including injection site pallor, coldness and hypoaesthesia or injury at the injection site resulting in bruising, bleeding, discoloration, erythema or skeletal injury.

OVERDOSAGE

Epinephrine is rapidly inactivated in the body and treatment following overdose with epinephrine is primarily supportive. If necessary, pressor effects may be counteracted by rapidly acting vasodilators or alpha-adrenergic blocking drugs. If prolonged hypotension follows such measure, it may be necessary to administer another pressor drug.

Overdosage of epinephrine may produce extremely elevated arterial pressure, which may result in cerebrovascular hemorrhage, particularly in elderly patients.

Overdosage may also result in pulmonary edema because of peripheral vascular constriction together with cardiac stimulation. Treatment consists of a rapidly acting alpha-adrenergic blocking drug and/or respiratory support.

Epinephrine overdosage can also cause transient bradycardia followed by tachycardia and these may be accompanied by potentially fatal cardiac arrhythmias. Premature ventricular contractions may appear within one minute after injection and may

be followed by multifocal ventricular tachycardia (prefibrillation rhythm). Subsidence of the ventricular effects may be followed by atrial tachycardia and occasionally by atrioventricular block. Treatment of arrhythmias consists of administration of a beta-blocking drug such as propranolol.

Overdosage sometimes results in extreme pallor and coldness of the skin, metabolic acidosis and kidney failure. Suitable corrective measures must be taken in such situations.

DOSAGE AND ADMINISTRATION

EpiPen[®] or EpiPen[®] Jr Auto-Injector prescribers should ensure that the patient or caregiver understands the indications and use of this product. A health care provider should review the patient instructions and operation of the EpiPen[®] or EpiPen[®] Jr Auto-Injector, in detail, with the patient or caregiver. Inject EpiPen[®] or EpiPen[®] Jr intramuscularly or subcutaneously into the anterolateral aspect of the thigh, through clothing if necessary. See detailed Directions for Use on the accompanying Patient Instructions.

Selection of the appropriate dosage strength is determined according to patient body weight.

EpiPen[®] Auto-Injector delivers 0.3 mg epinephrine injection (0.3 mL, 1:1000) and is intended for patients who weigh 30 kg or more (approximately 66 pounds or more).

EpiPen[®] Jr Auto-Injector delivers 0.15 mg epinephrine injection (0.3 mL, 1:2000) and is intended for patients who weigh 15 to 30 kg (33 – 66 pounds).

Each EpiPen[®] or EpiPen[®] Jr Auto-Injector contains a single dose of epinephrine. Since the doses of epinephrine delivered from EpiPen[®] or EpiPen[®] Jr Auto-Injector are fixed, consider using other forms of injectable epinephrine if doses lower than 0.15 mg are deemed necessary. The prescriber should carefully assess each patient to determine the most appropriate dose of epinephrine, recognizing the life-threatening nature of the reactions for which this drug is indicated. With severe persistent anaphylaxis, repeat injections with an additional EpiPen[®] Auto-Injector may be necessary.

Patients should be instructed to periodically visually inspect the epinephrine solution for particulate matter and discoloration. If the solution contains particulate matter or develops a pinkish color or becomes darker than slightly yellow, the patient should immediately contact their physician for a replacement, since these changes indicate that the effectiveness of the drug product may be decreased.

HOW SUPPLIED

EpiPen[®] Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) are available in individual cartons, NDC 49502-500-01, and as EpiPen 2-Pak[®], NDC 49502-500-02, a pack that contains two EpiPen[®] Auto-Injectors (epinephrine injections, USP, 1:1000, 0.3 mL) and one EpiPen[®] Auto-Injector trainer device.

EpiPen[®] Jr Auto-Injectors (epinephrine injection, USP, 1:2000, 0.3 mL) are available in individual cartons, NDC 49502-501-01, and as EpiPen Jr 2-Pak[®], NDC 49502-501-02, a pack that contains two EpiPen[®] Jr Auto-Injectors (epinephrine injections, USP, 1:2000, 0.3 mL) and one EpiPen[®] Auto-Injector trainer device.

EpiPen 2-Pak[®] and EpiPen Jr 2-Pak[®] also includes a S-clip to clip two cases together.

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F) (See USP Controlled Room Temperature). Contains no latex. Protect from light.

Rx only.

MANUFACTURED FOR Dey, L.P.,
NAPA, CALIFORNIA 94558, U.S.A.
by Meridian Medical Technologies, Inc.,
a subsidiary of King Pharmaceuticals[®], Inc.,
Columbia, MD 21046, U.S.A.

EpiPen[®], EpiPen[®] Jr, EpiPen 2-Pak[®], and EpiPen Jr 2-Pak[®] are registered trademarks of Mylan, Inc. licensed exclusively to its wholly-owned affiliate, Dey, L.P. of Napa California, USA.

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EMSAM®
(SELEGILINE TRANSDERMAL SYSTEM)
CONTINUOUS DELIVERY FOR ONCE-DAILY APPLICATION

Rx only

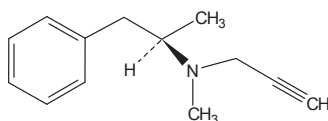
Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of EMSAM or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised for the need for close observation and communication with the prescriber. EMSAM is not approved for use in pediatric patients. Furthermore, EMSAM at any dose should not be used in children under the age of 12, even when administered with dietary modifications. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

DESCRIPTION

EMSAM® (selegiline transdermal system) is a transdermally administered antidepressant. When applied to intact skin, EMSAM is designed to continuously deliver selegiline over a 24-hour period.

Selegiline base is a colorless to yellow liquid, chemically described as (-)-(*M*)-Methyl-N-[(1*R*)-1-methyl-2-phenylethyl]prop-2-yn-1-amine. It has an empirical formula of C₁₃H₁₇N and a molecular weight of 187.30. The structural formula is:

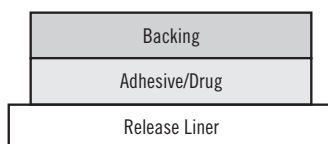


Selegiline Base

EMSAM systems are transdermal patches that contain 1 mg of selegiline per cm² and deliver approximately 0.3 mg of selegiline per cm² over 24 hours. EMSAM systems are available in three sizes: 20 mg/20 cm², 30 mg/30 cm², and 40 mg/40 cm² that deliver, on average, doses of 6 mg, 9 mg, or 12 mg, respectively, of selegiline over 24 hours.

EMSAM is a matrix-type transdermal system composed of three layers as illustrated in Figure 1 below. Layer 1 is the Backing Film that provides the matrix system with occlusivity and physical integrity and protects the adhesive/drug layer. Layer 2 is the Adhesive/Drug Layer. Layer 3 consists of side-by-side release liners that are peeled off and discarded by the patient prior to applying EMSAM. The inactive ingredients are acrylic adhesive, ethylene vinyl acetate/polyethylene, polyester, polyurethane, and silicone coated polyester.

Figure 1: Side view of EMSAM system. (Not to scale.)



CLINICAL PHARMACOLOGY

Pharmacodynamics

Selegiline (the drug substance of EMSAM) is an irreversible inhibitor of monoamine oxidase (MAO), an intracellular enzyme associated with the outer membrane of mitochondria. MAO exists as two isoenzymes, referred to as MAO-A and MAO-B. Selegiline has a greater affinity for MAO-B, compared to MAO-A. However, at antidepressant doses, selegiline inhibits both isoenzymes (see below).

The mechanism of action of EMSAM as an antidepressant is not fully understood, but is presumed to be linked to potentiation of monoamine neurotransmitter activity in the central nervous system (CNS) resulting from its inhibition of MAO activity. In an *in vivo* animal model used to test for antidepressant activity (Forced Swim Test), selegiline administered by transdermal patch exhibited antidepressant properties only at doses that inhibited both MAO-A and MAO-B activity in the brain. In the CNS, MAO-A and MAO-B play important roles in the catabolism of neurotransmitter amines such as norepinephrine, dopamine, and serotonin, as well as neuromodulators such as phenylethylamine. Other molecular sites of action have also been explored and in this regard, a direct pharmacological interaction may also occur between selegiline and brain neuronal α_{2B} receptors. In *in vitro* receptor binding assays, selegiline has demonstrated affinity for the human recombinant adrenergic α_{2B} receptor (K_i = 284 μM). No affinity [K_i > 10 μM] was noted at dopamine receptors, adrenergic β₁, glutamate, muscarinic M₁-M₅, nicotinic, or rolipram receptor/sites.

Pharmacokinetics

Absorption

Following dermal application of EMSAM to humans, 25% - 30% of the selegiline content on average is delivered systemically over 24 hours (range ~ 10% - 40%). Consequently, the degree of drug absorption may be 1/3 higher than the average amounts of 6 mg to 12 mg per 24 hours. Transdermal dosing results in substantially higher exposure to selegiline and lower exposure to metabolites compared to oral dosing, where extensive first-pass metabolism occurs (Figure 2). In a 10-day study with EMSAM administered to normal volunteers, steady-state selegiline plasma concentrations were achieved within 5 days of daily dosing. Absorption of selegiline is similar when EMSAM is applied to the upper torso or upper thigh. Mean (95% CI) steady-state plasma concentrations in healthy men and women following application of EMSAM to the upper torso or upper thigh are shown in Figure 3.

Figure 2: Average AUC_{inf} (ng•hr/mL) of selegiline and the three major metabolites estimated for a single, 24-hour application of an EMSAM 6 mg/24 hours patch and a single, 10 mg oral immediate release dose of selegiline HCl in 12 healthy male and female volunteers.

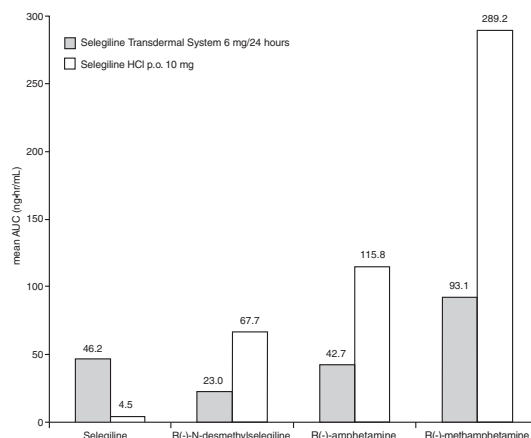
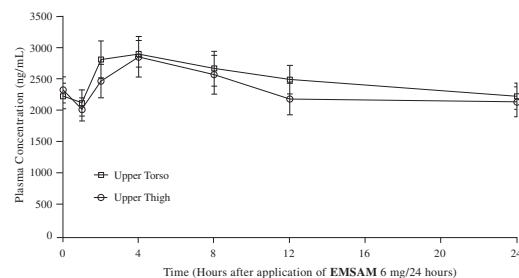


Figure 3: Average plasma (± 95% CI) selegiline concentrations in healthy male and female volunteers at steady-state after application of EMSAM 6 mg/24 hours to the upper torso.



Distribution

Following dermal application of radiolabeled selegiline to laboratory animals, selegiline is rapidly distributed to all body tissues. Selegiline rapidly penetrates the blood-brain barrier.

In humans, selegiline is approximately 90% bound to plasma protein over a 2 - 500 ng/mL concentration range. Selegiline does not accumulate in the skin.

In vivo Metabolism

Transdermally absorbed selegiline (via EMSAM) is not metabolized in human skin and does not undergo extensive first-pass metabolism. Selegiline is extensively metabolized by several CYP₄₅₀-dependent enzyme systems (see *In vitro Metabolism*). Selegiline is metabolized initially via N-dealkylation or N-depropargylation to form N-desmethylselegiline or R(-)-methamphetamine, respectively. Both of these metabolites can be further metabolized to R(-)-amphetamine. These metabolites are all levorotatory (l-) enantiomers and no racemic biotransformation to the dextrorotatory form (i.e., S(+)-amphetamine or S(+)-methamphetamine) occurs. R(-)-methamphetamine and R(-)-amphetamine are mainly excreted unchanged in urine.

In vitro Metabolism

In vitro studies utilizing human liver microsomes demonstrated that several CYP₄₅₀-dependent enzymes are involved in the metabolism of selegiline and its metabolites. CYP2B6, CYP2C9, and CYP3A4/5 appeared to be the major contributing enzymes in the formation of R(-)-methamphetamine from selegiline, with CYP2A6 having a minor role. CYP2A6, CYP2B6, and CYP3A4/5 appeared to contribute to the formation of R(-)-amphetamine from N-desmethylselegiline.

The potential for selegiline or N-desmethylselegiline to inhibit individual CYP₄₅₀-dependent enzyme pathways was also examined *in vitro* with human liver microsomes. Each substrate was examined over a concentration range of 2.5 to 250 μM. Consistent with competitive inhibition, both selegiline and N-desmethylselegiline caused a concentration dependent inhibition of CYP2D6 at 10 - 250 μM and CYP3A4/5 at 25 - 250 μM. CYP2C19 and CYP2B6 were also inhibited at concentrations ≥ 100 μM. All inhibitory effects of selegiline and N-desmethylselegiline occurred at concentrations that are several orders of magnitude higher than concentrations seen clinically (highest predose concentration observed at a dose of 12 mg/24 hours at steady-state was 0.046 μM) (see PRECAUTIONS, Drug Interactions).

Excretion

Approximately 10% and 2% of a radiolabeled dose applied dermally, as a DMSO solution, was recovered in urine and feces respectively, with at least 63% of the dose remaining unabsorbed. The remaining 25% of the dose was unaccounted for. Urinary excretion of unchanged selegiline accounted for 0.1% of the applied dose with the remainder of the dose recovered in urine being metabolites.

The systemic clearance of selegiline after intravenous administration was 1.4 L/min, and the mean half-lives of selegiline and its three metabolites, R(-)-N-desmethylselegiline, R(-)-amphetamine, and R(-)-methamphetamine, ranged from 18 - 25 hours.

Population Subgroups

Age -- The effect of age on the pharmacokinetics or metabolism of selegiline during administration of **EMSAM** has not been systematically evaluated. The recommended dose for elderly patients is **EMSAM 6 mg/24 hours**. (See **DOSAGE AND ADMINISTRATION**.)

Gender -- No gender differences have been observed in the pharmacokinetics or metabolism of selegiline during administration of **EMSAM**. No adjustment of **EMSAM** dosage based on gender is needed.

Reduced Hepatic Function

After a single administration of **EMSAM 6 mg/24 hours** in 8 patients with mild or moderate liver impairment (Child-Pugh classifications of A or B), no differences in either the metabolism or pharmacokinetic behavior of selegiline or its metabolites were observed as compared with data of normal subjects. No adjustment of **EMSAM** dosage is required in patients with moderate liver impairment.

Reduced Renal Function

Data from a single dose study examining the pharmacokinetics of **EMSAM 6 mg/24 hours** in 12 patients with renal impairment suggest that mild, moderate, or severe renal impairment does not affect the pharmacokinetics of selegiline after transdermal application. Therefore, no adjustment of **EMSAM** dosage is required in patients with renal impairment.

Dermal Adhesion

Dermal adhesion of **EMSAM** was examined after application of 6 mg/24 hours selegiline patches for 10 days to the upper torso. Approximately 88% - 89% of 6 mg/24 hours selegiline patches applied to the upper torso exhibited < 10% lift with approximately 6% - 7% of patches becoming detached.

External Heat

The effect of direct heat applied to the **EMSAM** patch on the bioavailability of selegiline has not been studied. However, in theory, heat may result in an increase in the amount of selegiline absorbed from the **EMSAM** patch and produce elevated serum levels of selegiline. Patients should be advised to avoid exposing the **EMSAM** application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Clinical Efficacy Trials

The efficacy of **EMSAM** as a treatment for major depressive disorder was established in two placebo-controlled studies of 6 and 8 weeks duration in adult outpatients (ages 18 to 70 years) meeting DSM-IV criteria for major depressive disorder. In both studies, patients were randomized to double-blind treatment with **EMSAM** or placebo. The 6-week trial (N = 176) showed that **EMSAM 6 mg/24 hours** was significantly more effective than placebo on the 17-item Hamilton Depression Rating Scale (HAM-D). In an 8-week dose titration trial, depressed patients (N = 265), who received **EMSAM** or placebo at a starting dose of 6 mg/24 hours, with possible increases to 9 mg/24 hours or 12 mg/24 hours based on clinical response, showed significant improvement compared with placebo on the primary outcome measure, the 28-item HAM-D total score.

In another trial, 322 patients meeting DSM-IV criteria for major depressive disorder who had responded during an initial 10-week open-label treatment phase for about 25 days, on average, to **EMSAM 6 mg/24 hours** were randomized either to continuation of **EMSAM** at the same dose (N = 159) or to placebo (N = 163) under double-blind conditions for observation of relapse. About 52% of the **EMSAM**-treated patients, as well as about 52% of the placebo-treated patients, had discontinued treatment by week 12 of the double-blind phase. Response during the open-label phase was defined as 17-item HAM-D score < 10 at either week 8 or 9 and at week 10 of the open-label phase. Relapse during the double-blind phase was defined as follows: (1) a 17-item HAM-D score \geq 14, (2) a CGI-S score of \geq 3 (with at least a 2-point increase from double-blind baseline), and (3) meeting DSM-IV criteria for major depressive disorder on two consecutive visits \geq 11 days apart. In the double-blind phase, patients receiving continued **EMSAM** experienced a significantly longer time to relapse.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

INDICATIONS AND USAGE

EMSAM (selegiline transdermal system) is indicated for the treatment of major depressive disorder.

The efficacy of **EMSAM** in the treatment of major depressive disorder was established in 6- and 8-week placebo-controlled trials of outpatients with diagnoses of DSM-IV category of major depressive disorder (see **Clinical Efficacy Trials**).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and suicide attempt or suicidal ideation.

The benefit of maintaining patients with major depressive disorder on therapy with **EMSAM** after

achieving a responder status for an average duration of about 25 days was demonstrated in a controlled trial (see **Clinical Efficacy Trials** under **CLINICAL PHARMACOLOGY**). The physician who elects to use **EMSAM** for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

The antidepressant action of **EMSAM** in hospitalized depressed patients has not been studied.

CONTRAINDICATIONS

EMSAM (selegiline transdermal system) is contraindicated in patients with known hypersensitivity to selegiline or to any component of the transdermal system.

EMSAM (selegiline transdermal system) is contraindicated with selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, and paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine); tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline); bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone, and propoxyphene; the antitussive agent dextromethorphan; St. John's wort; mirtazapine; and cyclobenzaprine. **EMSAM** should not be used with oral selegiline or other MAO inhibitors (MAOIs e.g., isocarboxazid, phenelzine, and tranylcypromine) (see **WARNINGS**).

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

As with other MAOIs, **EMSAM** is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine).

As with other MAOIs, patients taking **EMSAM** should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. **EMSAM** should be discontinued at least 10 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously.

As with other MAOIs, **EMSAM** is contraindicated for use in patients with pheochromocytoma.

EMSAM is an irreversible MAO inhibitor. As a class, these compounds have been associated with hypertensive crises caused by the ingestion of foods containing high amounts of tyramine. In its entirety, the data for **EMSAM 6 mg/24 hours** support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM 9 mg/24 hours** and **12 mg/24 hours**, patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9mg/24 hours and 12mg/24 hours**. (See **WARNINGS** and **PRECAUTIONS, Drug Interactions, Tyramine**.)

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorders (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressants in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1	
AGE RANGE	DRUG-PLACEBO DIFFERENCE IN NUMBER OF CASES OF SUICIDALITY PER 1,000 PATIENTS TREATED
	Increases Compared to Placebo
< 18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
\geq 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

Due to the limited data, EMSAM at any dose should not be used in children under the age of 12 years even when administered with dietary modifications. EMSAM is not approved for use in pediatric patients (See PRECAUTIONS/Pediatric Use).

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for EMSAM should be written for the smallest quantity of patches consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that EMSAM is not approved for use in treating bipolar depression.

Hypertensive Crisis

EMSAM is an irreversible MAO inhibitor. MAO is important in the catabolism of dietary amines (e.g., tyramine). In this regard, significant inhibition of intestinal MAO-A activity can impose a cardiovascular safety risk following the ingestion of tyramine-rich foods. As a class, MAOIs have been associated with hypertensive crises caused by the ingestion of foods with a high concentration of tyramine.

Hypertensive crises, which in some cases may be fatal, are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain. Intracranial bleeding has been reported in association with the increase in blood pressure. Patients should be instructed as to the signs and symptoms of severe hypertension and advised to seek immediate medical attention if these signs or symptoms are present.

In 6 of the 7 clinical studies conducted with EMSAM at doses of 6 mg/24 hours - 12 mg/24 hours, patients were not limited to a modified diet typically associated with this class of compounds. Although no hypertensive crises were reported as part of the safety assessment, the likelihood of developing this reaction cannot be fully determined since the amount of tyramine typically consumed during the course of treatment is not known and blood pressure was not continuously monitored.

To further define the likelihood of hypertensive crises with use of EMSAM, several Phase I tyramine challenge studies were conducted both with and without food (see PRECAUTIONS, Drug Interactions, Tyramine). In its entirety, the data for EMSAM 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for EMSAM 9 mg/24 hours, and the results from the Phase I tyramine challenge study in fed volunteers administered EMSAM 12 mg/24 hours (see PRECAUTIONS, Drug Interactions, Tyramine), patients receiving these doses should follow Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours.

If a hypertensive crisis occurs, EMSAM should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. Phentolamine 5 mg or labetalol 20 mg administered slowly intravenously is recommended therapy to control hypertension. Alternately, nitroprusside delivered by continuous intravenous infusion may be used. Fever should be managed by means of external cooling. Patients must be closely monitored until symptoms have stabilized.

Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours

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

Food and beverages to avoid and those which are acceptable¹:

Class of Food and Beverage	Tyramine-Rich Foods and Beverages to Avoid	Acceptable Foods and Drinks, Containing No or Little Tyramine
Meat, Poultry, and Fish	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring; and any spoiled or improperly stored meat, poultry, and fish (e.g., foods that have undergone changes in coloration, odor, or become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry, and fish, including fresh processed meats (e.g., lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese, and yogurt
Beverages	All varieties of tap beer and beers that have not been pasteurized so as to allow for ongoing fermentation	As with other antidepressants, concomitant use of alcohol with EMSAM is not recommended. (Bottled and canned beers and wines contain little or no tyramine.)
Miscellaneous	Concentrated yeast extract (e.g., Marmite), sauerkraut, most soybean products (including soy sauce and tofu), OTC supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain restaurant pizzas prepared with cheeses low in tyramine

¹Adapted from K.I. Shulman, S.E. Walker, Psychiatric Annals 2001; 31:378-384

Use With Other Drugs Affecting Monoamine Activity

Serious, sometimes fatal, central nervous system (CNS) toxicity referred to as the "serotonin syndrome" has been reported with the combination of non-selective MAOIs with certain other drugs, including tricyclic or selective serotonin reuptake inhibitor antidepressants, amphetamines, meperidine, or pentazocine. Serotonin syndrome is characterized by signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Similar less severe syndromes have been reported in a few patients receiving a combination of oral selegiline with one of these agents.

Therefore, EMSAM (selegiline transdermal system) should not be used in combination with selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine); tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline); oral selegiline or other MAOIs (e.g., isocarboxazid, phenelzine, and tranlycypromine); mirtazapine; bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone, and propoxyphene; the antitussive agent dextromethorphan; or St. John's wort because of the risk of life-threatening adverse reactions. Also, EMSAM should not be used with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropranolamine, and ephedrine). (See CONTRAINDICATIONS.)

Concomitant use of EMSAM with buspirone hydrochloride is not advised since several cases of elevated blood pressure have been reported in patients taking MAOIs who were then given buspirone HCl.

After stopping treatment with SSRIs; SNRIs; TCAs; MAOIs; meperidine and analgesics such as tramadol, methadone, and propoxyphene; dextromethorphan; St. John's wort; mirtazapine; bupropion HCl; or buspirone HCl, a time period equal to 4 - 5 half-lives (approximately 1 week) of the drug or any active metabolite should elapse before starting therapy with EMSAM. Because of the long half-life of fluoxetine and its active metabolite, at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with EMSAM. At least 2 weeks should elapse after stopping EMSAM before starting therapy with buspirone HCl or a drug that is contraindicated with EMSAM.

PRECAUTIONS

General

Hypotension

As with other MAOIs, postural hypotension, sometimes with orthostatic symptoms, can occur with EMSAM therapy. In short-term, placebo-controlled depression studies, the incidence of orthostatic hypotension (i.e., a decrease of 10 mmHg or greater in mean blood pressure when changing position from supine or sitting to standing) was 9.8% in EMSAM-treated patients and 6.7% in placebo-treated patients. It is recommended that elderly patients treated with EMSAM be closely observed for postural changes in blood pressure throughout treatment. Dose increases should be made cautiously in patients with pre-existing orthostasis. Postural hypotension may be relieved by having the patient recline until

the symptoms have abated. Patients should be cautioned to change positions gradually. Patients displaying orthostatic symptoms should have appropriate dosage adjustments as warranted.

Activation of Mania/Hypomania

During Phase III trials, a manic reaction occurred in 8/2036 (0.4%) patients treated with **EMSAM**. Activation of mania/hypomania can occur in a small proportion of patients with major affective disorder treated with other marketed antidepressants. As with all antidepressants, **EMSAM** should be used cautiously in patients with a history of mania.

Use in Patients With Concomitant Illness

Clinical experience with **EMSAM** in patients with certain concomitant systemic illnesses is limited. Caution is advised when using **EMSAM** in patients with disorders or conditions that can produce altered metabolism or hemodynamic responses.

EMSAM has not been systematically evaluated in patients with a history of recent myocardial infarction or unstable heart disease. Such patients were generally excluded from clinical studies during the product's premarketing testing.

No ECG abnormalities attributable to **EMSAM** were observed in clinical trials.

Although studies of phenylpropranolamine and pseudoephedrine did not reveal pharmacokinetic drug interactions with **EMSAM**, it is prudent to avoid the concomitant use of sympathomimetic agents, such as some decongestants.

Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with **EMSAM** and should counsel them in its appropriate use. A patient **Medication Guide** about "**Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions**" is available for **EMSAM**. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking **EMSAM**.

Clinical Worsening and Suicide Risk

Patients, their families and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment or when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly change in the medication.

General

Patients should be advised not to use oral selegiline while on **EMSAM** therapy.

Patients should be advised not to use carbamazepine or oxcarbazepine while on **EMSAM** therapy.

Patients should be advised not to use meperidine and analgesic agents such as tramadol, methadone, and propoxyphene.

Patients should be advised not to use sympathomimetic agents while on **EMSAM** therapy.

Patients should be advised not to use selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine, and St. John's wort), dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine), tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline), mirtazapine, oral selegiline or other MAOIs (e.g., isocarboxazid, phenelzine, and tranylcypromine), bupropion hydrochloride or bupropion hydrochloride while on **EMSAM** therapy.

EMSAM (selegiline transdermal system) has not been shown to impair psychomotor performance; however, any psychoactive drug may potentially impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that **EMSAM** therapy does not impair their ability to engage in such activities.

Patients should be told that, although **EMSAM** has not been shown to increase the impairment of mental and motor skills caused by alcohol, the concomitant use of **EMSAM** and alcohol in depressed patients is not recommended.

Patients should be advised to notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbals, because of the potential for drug interactions. Patients should also be advised to avoid tyramine-containing nutritional supplements and any cough medicine containing dextromethorphan.

Patients should be advised to use **EMSAM** exactly as prescribed. The need for dietary modifications at higher doses should be explained, and a brief description of hypertensive crisis provided. Rare hypertensive reactions with oral selegiline at doses recommended for Parkinson's disease and associated with dietary influences have been reported. The clinical relevance to **EMSAM** is unknown.

Patients should be advised that certain tyramine-rich foods and beverages should be avoided while on **EMSAM** 9 mg/24 hours or **EMSAM** 12 mg/24 hours, and for 2 weeks following discontinuation of **EMSAM** at these doses (see **CONTRAINDICATIONS** and **WARNINGS**).

Patients should be instructed to immediately report the occurrence of the following acute symptoms: severe headache, neck stiffness, heart racing or palpitations, or other sudden or unusual symptoms.

Patients should be advised to avoid exposing the **EMSAM** application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight since heat may result in an increase in the amount of selegiline absorbed from the **EMSAM** patch and produce elevated serum levels of selegiline.

Patients should be advised to change position gradually if lightheaded, faint, or dizzy while on **EMSAM** therapy.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during **EMSAM** therapy.

Patients should be advised to notify their physician if they are breast-feeding an infant.

While patients may notice improvement with **EMSAM** therapy in 1 to several weeks, they should be advised of the importance of continuing drug treatment as directed.

Patients should be advised not to cut the **EMSAM** system into smaller portions.

For instructions on how to use **EMSAM**, see **DOSAGE AND ADMINISTRATION, How to Use EMSAM**.

Drug Interactions

The potential for drug interactions between **EMSAM** and a variety of drugs was examined in several human studies. Drug interaction studies described below were conducted with **EMSAM** 6 mg/24 hours. Although no differences are expected, drug interaction studies have not been conducted at higher doses (see *In vitro* Metabolism). In all of the studies described below, no drug-related adverse events were noted that required discontinuation of any subjects. Further, the incidence and nature of the adverse events were consistent with those known for selegiline or the test agent.

Alcohol

The pharmacokinetics and pharmacodynamics of alcohol (0.75 mg/kg) alone or in combination with **EMSAM** 6 mg/24 hours for 7 days of treatment was examined in 16 healthy volunteers. No clinically significant differences were observed in the pharmacokinetics or pharmacodynamics of alcohol or the pharmacokinetics of selegiline during co-administration. Although **EMSAM** has not been shown to increase the impairment of mental and motor skills caused by alcohol (0.75 mg/kg) and failed to alter the pharmacokinetic properties of alcohol, patients should be advised that the use of alcohol is not recommended while taking **EMSAM**.

Alprazolam

In subjects who had received **EMSAM** 6 mg/24 hours for 7 days, co-administration with alprazolam (15 mg/day), a CYP3A4/5 substrate, did not affect the pharmacokinetics of either selegiline or alprazolam.

Carbamazepine

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 **EMSAM** 6 mg/24 hours in subjects who had received carbamazepine (400 mg/day) for 14 days. Changes in plasma selegiline concentrations were nearly two-fold, and variable across the subject population. The clinical relevance of these observations is unknown. Carbamazepine is contraindicated with MAOIs, including selegiline (see **CONTRAINDICATIONS**).

Ibuprofen

In subjects who had received **EMSAM** 6 mg/24 hours for 11 days, combined administration with the CYP2C9 substrate ibuprofen (800 mg single dose) did not affect the pharmacokinetics of either selegiline 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 **EMSAM** 6 mg/24 hours for 7 days and no differences in the pharmacokinetics of ketoconazole were observed.

Levothyroxine

In healthy subjects who had received **EMSAM** 6 mg/24 hours for 10 days, single dose administration with levothyroxine (150 µg) did not alter the pharmacokinetics of either selegiline or levothyroxine (as judged by T₃ and T₄ plasma levels).

Olanzapine

In subjects who had received **EMSAM** 6 mg/24 hours for 10 days, co-administration with olanzapine, a substrate for CYP1A2, CYP2D6, and possibly CYP2A6, did not affect the pharmacokinetics of either selegiline or olanzapine.

Phenylpropranolamine (PPA)

In subjects who had received **EMSAM** 6 mg/24 hours for 9 days, co-administration with PPA (25 mg every 4 hours for 24 hours) did not affect the pharmacokinetics of PPA. There was a higher incidence of significant blood pressure elevations with the co-administration of **EMSAM** and PPA than with PPA alone, suggesting a possible pharmacodynamic interaction. It is prudent to avoid the concomitant use of sympathomimetic agents with **EMSAM**.

Pseudoephedrine

EMSAM 6 mg/24 hours for 10 days, co-administered with pseudoephedrine (60 mg, 3 times a day) did not affect the pharmacokinetics of pseudoephedrine. The effect of pseudoephedrine on **EMSAM** was not examined. There were no clinically significant changes in blood pressure during pseudoephedrine administration alone, or in combination with **EMSAM**. Nonetheless, it is prudent to avoid the concomitant use of sympathomimetic agents with **EMSAM**.

Risperidone

In subjects who had received **EMSAM** 6 mg/24 hours for 10 days, co-administration with risperidone (2 mg per day for 7 days), a substrate for CYP2D6, did not affect the pharmacokinetics of either selegiline or risperidone.

Tyramine

Selegiline (the drug substance of **EMSAM**) is an irreversible inhibitor of monoamine oxidase (MAO), a ubiquitous intracellular enzyme. MAO exists as two isoenzymes, referred to as MAO-A and MAO-B. Selegiline shows greater affinity for MAO-B; however, as selegiline concentration increases, this selectivity is lost with resulting dose-related inhibition of MAO-A. Intestinal MAO is predominantly type A, while in the brain both isoenzymes exist.

MAO plays a vital physiological role in terminating the biological activity of both endogenous and exogenous amines. In addition to their role in the catabolism of monoamines in the CNS, MAOs are also important in the catabolism of exogenous amines found in a variety of foods and drugs. MAO in the gastrointestinal tract (primarily type A) provides protection from exogenous amines with vasopressor actions, such as tyramine, which if absorbed intact can cause a hypertensive crisis, the so-called "cheese reaction." If a large amount of tyramine is absorbed systemically, it is taken up by adrenergic neurons and causes norepinephrine release from neuronal storage sites with resultant elevation of blood pressure. While most foods contain negligible amounts or no tyramine, a few food products (see **WARNINGS**) may contain large amounts of tyramine that represent a potential risk for patients with significant inhibition of intestinal MAO-A resulting from administration of MAOIs. Tyramine-containing nutritional supplements should be avoided by patients taking **EMSAM** (selegiline transdermal system).

Animal studies have indicated the transdermal administration of selegiline via **EMSAM** 6 mg/24 hours allows for critical levels of MAO inhibition to be achieved in the brain while avoiding levels of gastrointestinal inhibition. To further define the risk of hypertensive crises with use of **EMSAM**, several Phase I tyramine challenge studies were conducted both with and without food.

Fourteen tyramine challenge studies including 214 healthy subjects (age range 18 - 65; 31 subjects > 50 years of age) were conducted to determine the pressor effects of oral tyramine with concurrent **EMSAM** treatment (6 mg/24 hours - 12 mg/24 hours), measured as the dose of tyramine required to raise systolic blood pressure by 30 mmHg (TYR30). Studies were conducted with and without concomitant administration of food. Studies conducted with food are most relevant to clinical practice since tyramine typically will be consumed in food. A high-tyramine meal is considered to contain up to 40 mg of tyramine.

One study using a crossover design in 13 subjects investigated tyramine pressor doses (TYR30) after administration of **EMSAM** 6 mg/24 hours and oral selegiline (5 mg twice daily) for 9 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 338 mg and 385 mg in subjects treated with **EMSAM** and oral selegiline, respectively.

Another study using a crossover design in 10 subjects investigated tyramine pressor doses after administration of **EMSAM** 6 mg/24 hours or tranlycypromine 30 mg/day for 10 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 270 mg in subjects treated with **EMSAM** 6 mg/24 hours and 10 mg in subjects treated with tranlycypromine.

In a third crossover study, tyramine without food was administered to 12 subjects. The mean tyramine pressor doses (TYR30) after administration of **EMSAM** 6 mg/24 hours for 9 and 33 days were 292 mg and 204 mg, respectively. The lowest pressor dose was 50 mg in one subject in the 33-day group.

Tyramine pressor doses were also studied in 11 subjects after extended treatment with **EMSAM** 12 mg/24 hours. At 30, 60, and 90 days, the mean pressor doses (TYR30) of tyramine administered without food were 95 mg, 72 mg, and 88 mg, respectively. The lowest pressor dose without food was 25 mg in 3 subjects at day 30 while on **EMSAM** 12 mg/24 hours. Eight subjects from this study, with a mean tyramine pressor dose of 64 mg at 90 days, were subsequently administered tyramine with food, resulting in a mean pressor dose of 172 mg (2.7 times the mean pressor dose observed without food, $p < 0.003$).

With the exception of one study (N = 153), the Phase III clinical development program was conducted without requiring a modified diet (N = 2553, 1606 at 6 mg/24 hours, and 947 at 9 mg/24 hours or 12 mg/24 hours). No hypertensive crises were reported in any patient receiving **EMSAM**.

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

Warfarin

Warfarin is a substrate for CYP2C9 and CYP3A4 metabolism pathways. In healthy volunteers titrated with Coumadin® (warfarin sodium) to clinical levels of anticoagulation (INR of 1.5 to 2), co-administration with **EMSAM** 6 mg/24 hours for 7 days did not affect the pharmacokinetics of the individual warfarin enantiomers. **EMSAM** did not alter the clinical pharmacodynamic effects of warfarin as measured by INR, Factor VII or Factor X levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In an oral carcinogenicity study in rats, selegiline given in the diet for 104 weeks was not carcinogenic up to the highest evaluable dose tested (3.5 mg/kg/day, which is 3 times the oral maximum recommended human dose on a mg/m² basis).

Carcinogenicity studies have not been conducted with transdermal administration of selegiline.

Mutagenesis

Selegiline induced mutations and chromosomal damage when tested in the *in vitro* mouse lymphoma

assay with and without metabolic activation. Selegiline was negative in the Ames assay, the *in vitro* mammalian chromosome aberration assay in human lymphocytes, and the *in vivo* oral mouse micronucleus assay.

Impairment of Fertility

A mating and fertility study was conducted in male and female rats at transdermal doses of 10, 30, and 75 mg/kg/day of selegiline (8, 24, and 60 times the maximum recommended human dose of **EMSAM** [12 mg/24 hours] on a mg/m² basis). Slight decreases in sperm concentration and total sperm count were observed at the high dose; however, no significant adverse effects on fertility or reproductive performance were observed.

Teratogenic Effects - Pregnancy Category C

In an embryofetal development study in rats, dams were treated with transdermal selegiline during the period of organogenesis at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the maximum recommended human dose [MRHD] of **EMSAM** [12 mg/24 hours] on a mg/m² basis). At the highest dose there was a decrease in fetal weight and slight increases in malformations, delayed ossification (also seen at the mid dose), and embryofetal post-implantation lethality. Concentrations of selegiline and its metabolites in fetal plasma were generally similar to those in maternal plasma. In an *oral* embryofetal development study in rats, a decrease in fetal weight occurred at the highest dose tested (36 mg/kg; no-effect dose 12 mg/kg); no increase in malformations was seen.

In an embryofetal development study in rabbits, dams were treated with transdermal selegiline during the period of organogenesis at doses of 2.5, 10, and 40 mg/kg/day (4, 16, and 64 times the MRHD on a mg/m² basis). A slight increase in visceral malformations was seen at the high dose. In an *oral* embryofetal development study in rabbits, increases in total resorptions and post-implantation loss, and a decrease in the number of live fetuses per dam, occurred at the highest dose tested (50 mg/kg; no-effect dose 25 mg/kg).

In a prenatal and postnatal development study in rats, dams were treated with transdermal selegiline at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the MRHD on a mg/m² basis) on days 6 - 21 of gestation and days 1 - 21 of the lactation period. An increase in post-implantation loss was seen at the mid and high doses, and an increase in stillborn pups was seen at the high dose. Decreases in pup weight (throughout lactation and post-weaning periods) and survival (throughout lactation period), retarded pup physical development, and pup epididymal and testicular hypoplasia, were seen at the mid and high doses. Retarded neurobehavioral and sexual development was seen at all doses. Adverse effects on pup reproductive performance, as evidenced by decreases in implantations and litter size, were seen at the high dose. These findings suggest persistent effects on the offspring of treated dams. A no-effect dose was not established for developmental toxicity. In this study, concentrations of selegiline and its metabolites in milk were ~ 15 and 5 times, respectively, the concentrations in plasma, indicating that the pups were directly dosed during the lactation period.

There are no adequate and well-controlled studies in pregnant women. **EMSAM** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of **EMSAM** on labor and delivery in humans is unknown.

Nursing Mothers

In a prenatal and postnatal study of transdermal selegiline in rats, selegiline and metabolites were excreted into the milk of lactating rats. The levels of selegiline and metabolites in milk were approximately 15 and 5 times, respectively, steady-state levels of selegiline and metabolites in maternal plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised administering **EMSAM** to a nursing mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS, Clinical Worsening and Suicide Risk**).

Anyone considering the use of **EMSAM** (selegiline transdermal system) in a child or adolescent must balance the potential risks with the clinical need.

Due to limited data, **EMSAM** at any dose should not be used in children under the age of 12 years even when administered with dietary modifications. **EMSAM** is not approved for use in pediatric patients.

Commercially available doses of **EMSAM** have not been studied in children under the age of 12 years. Limited pharmacokinetic data with lower doses than in the commercially available formulations suggest that children under the age of 12 years treated with **EMSAM** may be exposed to increased levels of selegiline compared to adolescents or adults. Therefore, the possibility exists for an increased risk of hypertensive crisis, even at the lowest dose of commercially available **EMSAM**, when administered without dietary modifications.

Geriatric Use

One hundred ninety-eight (198) elderly (≥ 65 years of age) patients participated in clinical studies with **EMSAM** 6 mg/24 hours to 12 mg/24 hours. There were no overall differences in effectiveness between elderly and younger patients. In short-term, placebo-controlled depression trials, patients age 50 and older appeared to be at higher risk for rash (4.4% **EMSAM** vs. 0% placebo) than younger patients (3.4% **EMSAM** vs. 2.4% placebo).

ADVERSE EVENTS

The premarketing development program for **EMSAM** included selegiline exposures in patients and/or normal subjects from two different groups of studies: 702 healthy subjects in clinical pharmacology/pharmacokinetics studies and 2036 exposures from patients in controlled and uncontrolled major depressive disorder clinical trials. The conditions and duration of treatment with **EMSAM** varied and

included double-blind, open-label, fixed-dose, and dose titration studies of short-term and longer-term exposures. Safety was assessed by monitoring adverse events, physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term Placebo-Controlled Trials

Adverse Events Associated with Discontinuation of Treatment

Among 817 depressed patients who received **EMSAM** at doses of either 3 mg/24 hours (151 patients), 6 mg/24 hours (550 patients) or 6 mg/24 hours, 9 mg/24 hours, and 12 mg/24 hours (116 patients) in placebo-controlled trials of up to 8 weeks in duration, 7.1% discontinued treatment due to an adverse event as compared with 3.6% of 668 patients receiving placebo. The only adverse event associated with discontinuation, in at least 1% of **EMSAM**-treated patients at a rate at least twice that of placebo, was application site reaction (2% **EMSAM** vs. 0% placebo).

Adverse Events Occurring at an Incidence of 2% or More Among **EMSAM**-Treated Patients

Table 2 enumerates adverse events that occurred at an incidence of 2% or more (rounded to the nearest percent) among 817 depressed patients who received **EMSAM** in doses ranging from 3 to 12 mg/24 hours in placebo-controlled trials of up to 8 weeks in duration. Events included are those occurring in 2% or more of patients treated with **EMSAM** and for which the incidence in patients treated with **EMSAM** was greater than the incidence in placebo-treated patients.

Only one adverse event was associated with a reporting of at least 5% in the **EMSAM** group, and a rate at least twice that in the placebo group, in the pool of short-term, placebo-controlled studies: application site reactions (see [Application Site Reactions](#), below). In one such study which utilized higher mean doses of **EMSAM** than that in the entire study pool, the following events met these criteria: application site reactions, insomnia, diarrhea, and pharyngitis.

These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physicians with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 2. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder With **EMSAM¹**

Body System/Preferred Term	EMSAM (N = 817)	Placebo (N = 668)
(% of Patients Reporting Event)		
Body as a Whole		
Headache	18	17
Digestive		
Diarrhea	9	7
Dyspepsia	4	3
Nervous		
Insomnia	12	7
Dry Mouth	8	6
Respiratory		
Pharyngitis	3	2
Sinusitis	3	1
Skin		
Application Site Reaction	24	12
Rash	4	2

¹Events reported by at least 2% of patients treated with **EMSAM** are included, except the following events, which had an incidence on placebo treatment \geq **EMSAM**: infection, nausea, dizziness, pain, abdominal pain, nervousness, back pain, asthenia, anxiety, flu syndrome, accidental injury, somnolence, rhinitis, and palpitations.

Application Site Reactions

In the pool of short-term, placebo-controlled major depressive disorder studies, application site reactions (ASRs) were reported in 24% of **EMSAM**-treated patients and 12% of placebo-treated patients. Most ASRs were mild or moderate in severity. None were considered serious. ASRs led to dropout in 2% of **EMSAM**-treated patients and no placebo-treated patients.

In one such study which utilized higher mean doses of **EMSAM**, ASRs were reported in 40% of **EMSAM**-treated patients and 20% of placebo-treated patients. Most of the ASRs in this study were described as erythema and most resolved spontaneously, requiring no treatment. When treatment was administered, it most commonly consisted of dermatological preparations of corticosteroids.

Male and Female Sexual Dysfunction with MAO Inhibitors

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 3 shows that the incidence rates of sexual side effects in patients with major depressive disorder are comparable to the placebo rates in placebo-controlled trials.

Table 3. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials With **EMSAM**

Adverse Event	EMSAM	Placebo
IN MALES ONLY		
	(N = 304)	(N = 256)
Abnormal Ejaculation	1.0%	0.0%
Decreased Libido	0.7%	0.0%
Impotence	0.7%	0.4%
Anorgasmia	0.2%	0.0%
IN FEMALES ONLY		
	(N = 513)	(N = 412)
Decreased Libido	0.0%	0.2%

There are no adequately designed studies examining sexual dysfunction with **EMSAM** treatment.

Vital Sign Changes

EMSAM and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure), and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. In the pool of short-term, placebo-controlled major depressive disorder studies, 3.0% of **EMSAM**-treated patients and 1.5% of placebo-treated patients experienced a low systolic blood pressure, defined as a reading less than or equal to 90 mmHg with a change from baseline of at least 20 mmHg. In one study which utilized higher mean doses of **EMSAM**, 6.2% of **EMSAM**-treated patients and no placebo-treated patients experienced a low standing systolic blood pressure by these criteria.

In the pool of short-term major depressive disorder trials, 9.8% of **EMSAM**-treated patients and 6.7% of placebo-treated patients experienced a notable orthostatic change in blood pressure, defined as a decrease of at least 10 mmHg in mean blood pressure with postural change.

Weight Changes

In placebo-controlled studies (6 - 8 weeks), the incidence of patients who experienced \geq 5% weight gain or weight loss is shown in Table 4.

Table 4. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials With **EMSAM**

Weight Change	EMSAM	Placebo
	(N = 757)	(N = 614)
Gained \geq 5%	2.1%	2.4%
Lost \geq 5%	5.0%	2.8%

In these trials, the mean change in body weight among **EMSAM**-treated patients was -1.2 lbs compared to + 0.3 lbs in placebo-treated patients.

Laboratory Changes

EMSAM and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with **EMSAM**.

ECG Changes

Electrocardiograms (ECGs) from **EMSAM** (N = 817) and placebo (N = 668) groups in controlled studies were compared with respect to (1) mean change from baseline in various ECG parameters, and (2) the incidence of patients meeting criteria for clinically significant changes from baseline in these variables.

No clinically meaningful changes in ECG parameters from baseline to final visit were observed for patients in controlled studies.

Other Events Observed During the Premarketing Evaluation of **EMSAM**

During the premarketing assessment in major depressive disorder, **EMSAM** was administered to 2036 patients in Phase III studies. The conditions and duration of exposure to **EMSAM** varied and included double-blind and open-label studies.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. All reported adverse events are included except those already listed in Table 2 or elsewhere in labeling, and those events occurring in only one patient. It is important to emphasize that

although the events occurred during treatment with EMSAM, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: *Frequent:* Chest pain, neck pain. *Infrequent:* Bacterial infection, fever, cyst, fungal infection, chills, viral infection, suicide attempt, neck rigidity, pelvic pain, photosensitivity reaction, face edema, flank pain, hernia, intentional injury, neoplasm, generalized edema, overdose. *Rare:* Body odor, halitosis, heat stroke, parasitic infection, malaise, moniliasis.

Cardiovascular System: *Frequent:* Hypertension. *Infrequent:* Vasodilatation, tachycardia, migraine, syncope, atrial fibrillation, peripheral vascular disorder. *Rare:* Myocardial infarct.

Digestive System: *Frequent:* Constipation, flatulence, anorexia, gastroenteritis, vomiting. *Infrequent:* Increased appetite, thirst, periodontal abscess, eructation, gastritis, colitis, dysphagia, tongue edema, glossitis, increased salivation, abnormal liver function tests, melena, tongue disorder, tooth caries. *Rare:* GI neoplasia, rectal hemorrhage.

Hemic and Lymphatic System: *Frequent:* Ecchymosis. *Infrequent:* Anemia, lymphadenopathy. *Rare:* Leukocytosis, leukopenia, petechia.

Metabolic and Nutritional: *Frequent:* Peripheral edema. *Infrequent:* Hyperglycemia, increased SGPT, edema, hypercholesterolemia, increased SGOT, dehydration, alcohol intolerance, hyponatremia, increased lactic dehydrogenase. *Rare:* Increased alkaline phosphatase, bilirubinemia, hypoglycemic reaction.

Musculoskeletal System: *Frequent:* Myalgia, pathological fracture. *Infrequent:* Arthralgia, generalized spasm, arthritis, myasthenia, arthrosis, tenosynovitis. *Rare:* Osteoporosis.

Nervous System: *Frequent:* Agitation, paresthesia, thinking abnormal, amnesia. *Infrequent:* Leg cramps, tremor, vertigo, hypertonia, twitching, emotional lability, confusion, manic reaction, depersonalization, hyperkinesias, hostility, myoclonus, circumoral paresthesia, hyperesthesia, increased libido, euphoria, neurosis, paranoid reaction. *Rare:* Ataxia.

Respiratory System: *Frequent:* Cough increased, bronchitis. *Infrequent:* Dyspnea, asthma, pneumonia, laryngismus. *Rare:* Epistaxis, laryngitis, yawn.

Skin and Appendages: *Frequent:* Pruritus, sweating, acne. *Infrequent:* Dry skin, maculopapular rash, contact dermatitis, urticaria, herpes simplex, alopecia, vesiculobullous rash, herpes zoster, skin hypertrophy, fungal dermatitis, skin benign neoplasm. *Rare:* Eczema.

Special Senses: *Frequent:* Taste perversion, tinnitus. *Infrequent:* Dry eyes, conjunctivitis, ear pain, eye pain, otitis media, parosmia. *Rare:* Mydriasis, otitis external, visual field defect.

Urogenital System: *Frequent:* Urinary tract infection, urinary frequency, dysmenorrhea, metrorrhagia. *Infrequent:* Urinary tract infection (male), vaginitis, cystitis (female), hematuria (female), unintended pregnancy, dysuria (female), urinary urgency (male and female), vaginal moniliasis, menorrhagia, urination impaired (male), breast neoplasm (female), kidney calculus (female), vaginal hemorrhage, amenorrhea, breast pain, polyuria (female).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

EMSAM (selegiline transdermal system) is not a controlled substance.

Physical and Psychological Dependence

Several animal studies have assessed potential for abuse and/or dependence with chronic selegiline administration. None of these studies demonstrated a potential for selegiline abuse or dependence.

EMSAM has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of EMSAM misuse or abuse (e.g., development of tolerance, increases in dose, or drug-seeking behavior).

OVERDOSAGE

There are no specific antidotes for EMSAM. If symptoms of overdosage occur, immediately remove the EMSAM system and institute appropriate supportive therapy. For contemporary consultation on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222.

EMSAM is considered to be an irreversible MAOI at therapeutic doses and, in overdosage, is likely to cause excessive MAO-A inhibition, and may result in the signs and symptoms resembling overdosage with other non-selective, oral MAOI antidepressants [e.g., tranylcypromine (Parnate®), phenelzine (Nardil®), or isocarboxazide (Marplan®)].

Overdosage with Non-Selective MAO Inhibition

NOTE: The following is provided for reference only; it does not describe events that have actually been observed with selegiline in overdosage. No information regarding overdose by ingestion of EMSAM is available.

Typical signs and symptoms associated with overdosage of non-selective MAOI antidepressants may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of

signs may occur, and peak effects may not be observed for 24 - 48 hours. Since death has been reported following overdosage with MAOI agents, hospitalization with close monitoring during this period is essential.

Overdosage with MAOI agents is typically associated with CNS and cardiovascular toxicity. Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, convulsions, coma, rapid and irregular pulse, hypertension, hypotension and vascular collapse, precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin. Type and intensity of symptoms may be related to extent of the overdosage.

Treatment should include supportive measures, with pharmacological intervention as appropriate. Symptoms may persist after drug washout because of the irreversible inhibitory effects of these agents on systemic MAO activity. With overdosage, in order to avoid the occurrence of hypertensive crisis ("cheese reaction"), dietary tyramine should be restricted for several weeks beyond recovery to permit regeneration of the peripheral MAO-A isoenzyme.

DOSAGE AND ADMINISTRATION

Initial Treatment

EMSAM should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm once every 24 hours. The recommended starting dose and target dose for EMSAM is 6 mg/24 hours. EMSAM has been systematically evaluated and shown to be effective in a dose range of 6 mg/24 hours to 12 mg/24 hours. However, the trials were not designed to assess if higher doses are more effective than the lowest effective dose of 6 mg/24 hours. Based on clinical judgment, if dose increases are indicated for individual patients, they should occur in dose increments 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 antidepressant drugs, full antidepressant effect may be delayed.

Patients should be informed that tyramine-rich foods and beverages should be avoided beginning on the first day of EMSAM 9 mg/24 hours or 12 mg/24 hours treatment and should continue to be avoided for 2 weeks after a dose reduction to EMSAM 6 mg/24 hours or following the discontinuation of EMSAM 9 mg/24 hours or 12 mg/24 hours (see WARNINGS).

Special Populations

EMSAM at any dose should not be used in children under the age of 12 years even when administered with dietary modifications. EMSAM is not approved for use in pediatric patients.

No dosage adjustment is required for patients with mild to moderate renal or hepatic impairment. The recommended dose for elderly patients (≥ 65 years) is EMSAM 6 mg/24 hours daily. Dose increases, in the elderly, should be made with caution and patients should be closely observed for postural changes in blood pressure throughout treatment.

How to Use EMSAM

- EMSAM should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm. A new application site should be selected with each new patch to avoid re-application to the same site on consecutive days. Patches should be applied at approximately the same time each day.
- Apply the patch to an area of skin that is not hairy, oily, irritated, broken, scarred or calloused. Do not place the patch where your clothing is tight, which could cause the patch to rub off.
- After you have selected the site for your patch, wash the area gently and thoroughly with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.
- Just before you apply the patch, remove it from the pouch. Remove half of the protective backing and throw it away. Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers.
- Press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface.
- After you have applied the patch, wash your hands thoroughly with soap and water to remove any medicine that may have gotten on them. Do not touch your eyes until after you have washed your hands.
- After 24 hours, remove the patch. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.
- Throw away the folded patch so that children and/or pets cannot reach it.
- Wash your hands with soap and water.
- If your patch falls off, apply a new patch to a new site and resume your previous schedule.
- Only one EMSAM patch should be worn at a time.
- Avoid exposing the EMSAM application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Maintenance Treatment

It is generally agreed that episodes of depression require several months or longer of sustained pharmacologic therapy. The benefit of maintaining depressed patients on therapy with EMSAM at a dose of 6 mg/24 hours after achieving a responder status for an average duration of about 25 days was

demonstrated in a controlled trial (see **Clinical Efficacy Trials** and **INDICATIONS AND USAGE**). The physician who elects to use **EMSAM** for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

HOW SUPPLIED

EMSAM (selegiline transdermal system) is supplied as 6 mg/24 hours (20 mg/20 cm²), 9 mg/24 hours (30 mg/30 cm²) and 12 mg/24 hours (40 mg/40 cm²) transdermal systems.

They are available as:

NDC 49502-900-30: 6 mg/24 hours (20 mg/20 cm²) box of 30 transdermal systems.

NDC 49502-901-30: 9 mg/24 hours (30 mg/30 cm²) box of 30 transdermal systems.

NDC 49502-902-30: 12 mg/24 hours (40 mg/40 cm²) box of 30 transdermal systems.

STORAGE AND DISPOSAL

Store at 20° to 25° C (68° to 77° F). [See USP Controlled Room Temperature.] Do not store outside of the sealed pouch. Apply immediately upon removal from the protective pouch. Discard used **EMSAM** in household trash in a manner that prevents accidental application or ingestion by children, pets or others.

DISTRIBUTED BY:



MANUFACTURED FOR:



MAY 2009

EMSAM:PIR7
03-943-00B

MEDICATION GUIDE EMSAM® [EM sam]

Generic Name: selegiline transdermal system

Rx only

Read this Medication Guide carefully before you start using EMSAM and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about EMSAM, ask your doctor or pharmacist.

IMPORTANT: Be sure to read the section of this Medication Guide beginning with “What is the most important information I should know about EMSAM?” It contains important information about certain changes in diet that might be needed, other medications to avoid, and other important information about this medication. It immediately follows the next section called Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions.

Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member’s antidepressant medicine. This section of the Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. Talk to your, or your family member’s, healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illnesses

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.
2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
 - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
 - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
 - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- Antidepressant medicines have other side effects. Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- Antidepressant medicines can interact with other medicines. Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child’s healthcare provider for more information.

ABOUT USING ANTIDEPRESSANTS IN CHILDREN AND TEENAGERS

EMSAM at any dose should not be used in children under the age of 12 years even when administered with dietary modifications. EMSAM is not approved for use in pediatric patients.

What is the most important information I should know about EMSAM?

1. EMSAM (selegiline transdermal system) contains a medicine called a monoamine oxidase inhibitor, also called a MAOI. MAOI medicines, including EMSAM, can cause a sudden, large increase in blood pressure (hypertensive crisis) if you eat foods and drinks that contain high amounts of tyramine. A hypertensive crisis can be a life-threatening condition. See “What are the possible side effects of EMSAM?” for signs and symptoms of a hypertensive crisis.
- EMSAM comes in three different doses and patch sizes:
 - a 6 mg/24 hours patch
 - a 9 mg/24 hours patch
 - a 12 mg/24 hours patch
 - You must avoid (not eat or drink) certain foods and drinks while using EMSAM 9 mg/24 hours and EMSAM 12 mg/24 hours patches and for 2 weeks after stopping EMSAM 9 mg/24 hours and EMSAM 12 mg/24 hours patches. (The table below lists these foods and drinks.) The table also lists foods and drinks that are okay to eat and drink while using EMSAM 9 mg/24 hours and EMSAM 12 mg/24 hours patches.
 - You do not have to make any diet changes with the EMSAM 6 mg/24 hours patch.

Type of Food and Drink	Tyramine-Rich Foods and Drinks to Avoid	Acceptable Foods and Drinks, Containing No or Little Tyramine
<u>Meat, Poultry, and Fish</u>	<ul style="list-style-type: none">• Air dried, aged and fermented meats, sausages and salamis• Pickled herring• Any spoiled or improperly stored meat, poultry, and fish. These are foods that have a change in color, odor, or become moldy.• Spoiled or improperly stored animal livers	<ul style="list-style-type: none">• Fresh meat, poultry, and fish, including fresh processed meats (such as lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
<u>Vegetables</u>	<ul style="list-style-type: none">• Broad bean pods (fava bean pods)	<ul style="list-style-type: none">• All other vegetables
<u>Dairy (milk products)</u>	<ul style="list-style-type: none">• Aged cheeses	<ul style="list-style-type: none">• Processed cheeses, mozzarella, ricotta cheese, cottage cheese, and yogurt
<u>Drinks</u>	<ul style="list-style-type: none">• All tap beers and other beers that have not been pasteurized	<ul style="list-style-type: none">• As with other antidepressants, concomitant use of alcohol with EMSAM is not recommended. (Bottled and canned beers and wines contain little or no tyramine.)
<u>Other</u>	<ul style="list-style-type: none">• Concentrated yeast extract (such as Marmite)• Sauerkraut• Most soybean products (including soy sauce and tofu)• Over-the-counter supplements containing tyramine	<ul style="list-style-type: none">• Brewer’s yeast, baker’s yeast• Soy milk• Pizzas from commercial chain restaurants prepared with cheeses low in tyramine

¹Adapted from K.I. Shulman, S.E. Walker, Psychiatric Annals 2001; 31:378-384

- All foods you eat must be fresh or properly frozen.
 - Avoid foods when you do not know their storage conditions.
2. EMSAM can cause serious and potentially life-threatening reactions if used with certain other medicines. Do not take the following medicines while using EMSAM, and for 2 weeks after stopping EMSAM:
 - other medicines to treat depression (antidepressants) including other MAOI medicines
 - medicine which contains selegiline (such as Eldepryl®)
 - St. John’s wort (a herbal supplement)
 - Demerol® (meperidine), or medicines that contain meperidine (a narcotic pain medicine) or the pain medicines tramadol, methadone, or propoxyphene
 - Tegretol® (carbamazepine), or other medicines that contain carbamazepine (a seizure medicine)
 - Trileptal® (oxcarbazepine), or other medicines that contain oxcarbazepine (a seizure medicine)
 - Cold or cough preparations that contain dextromethorphan
 - Flexeril® or other medicines that contain cyclobenzaprine (a medicine used to treat muscle spasms)

- decongestant medicines, found in many products to treat cold symptoms
- over-the-counter diet pills or herbal weight-loss products
- any herbal or dietary supplement that contains tyramine
- medicines called amphetamines, also called stimulants or “uppers”
- BuSpar® (buspirone HCl), an anxiety medicine

Some of these medicines will have to be stopped for at least a week before you can start using EMSAM.

What is EMSAM?

EMSAM is a skin patch (transdermal system) used to treat major depression. The skin patch delivers the medicine through your skin and into your bloodstream.

EMSAM has not been studied for the treatment of depression in children under 18 years of age.

Who should not use EMSAM?

Do not use EMSAM (selegiline transdermal system) if you are:

- taking certain other medicines. See “What is the most important information I should know about EMSAM?”
- allergic to anything in EMSAM. See the end of this Medication Guide for a complete list of ingredients in EMSAM.

What should I tell my doctor before starting EMSAM?

Tell your doctor about all your medical conditions, including if you:

- have any heart problems
- have or had manic episodes (a mental condition that causes “high” moods)
- have or had seizures (convulsions or “fits”)
- tend to get dizzy or faint
- are pregnant or planning to become pregnant. It is not known if EMSAM can harm your unborn baby.
- are breast-feeding. It is not known if EMSAM passes into your milk or if it can harm your baby.

Tell your doctor about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. EMSAM can cause a serious and life-threatening reaction if used with certain other medicines. See “What is the most important information I should know about EMSAM?”

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist. Do not take any new medicine while using EMSAM, and for 2 weeks after you stop using it, before talking with your doctor.

How should I use EMSAM?

See the end of this Medication Guide for “How to Use and Apply an EMSAM Patch”.

- Use EMSAM exactly as prescribed by your doctor. Use only one patch at a time. Change the patch once a day (every 24 hours). Choose a time of day that works best for you.
- Your doctor will prescribe a dose of EMSAM (selegiline transdermal system) based on your condition. Your doctor may change your dose if needed.
- Talk to your doctor often about your condition. You may notice an improvement in your condition with EMSAM therapy after several weeks. Do not stop or change your treatment with EMSAM without talking to your doctor.
- Make sure you do not eat foods or drink beverages that contain high amounts of tyramine while using EMSAM 9 mg/24 hours or EMSAM 12 mg/24 hours patches, and for 2 weeks after you stop using them.
- If you use more than one EMSAM patch at a time, remove EMSAM patches right away and call your doctor or local Poison Control Center.
- Avoid exposing the EMSAM application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.
- Tell your doctor if you plan to have surgery. Also, tell your surgeon that you take EMSAM. EMSAM should be stopped 10 days before you have elective surgery.

What should I avoid while using EMSAM?

- You must not eat foods or drink beverages that contain high amounts of tyramine while using EMSAM 9 mg/24 hours and 12 mg/24 hours patches. You do not have to make any diet changes with the EMSAM 6 mg/24 hours patch. See “What is the most important information I should know about EMSAM?”
- Do not take other medicines while using EMSAM or for 2 weeks after you stop using it unless your doctor has told you it is okay. See “What is the most important information I should know about EMSAM?”
- Do not drive or operate dangerous machinery until you know how EMSAM affects you. EMSAM may reduce your judgment, ability to think, or coordination.
- Drinking alcoholic beverages is not recommended while using EMSAM.

What are the possible side effects of EMSAM?

EMSAM:

- can cause a sudden, large increase in blood pressure (“hypertensive crisis”) if you eat certain foods and drinks during treatment. See “What is the most important information I should know about EMSAM?” A hypertensive crisis can lead to stroke and death. Symptoms of a hypertensive crisis include the sudden onset of severe headache, nausea, stiff neck, a fast heartbeat or a change in the way your heart beats (palpitations), a lot of sweating, and confusion. If you suddenly have these symptoms, get medical care right away.
- can cause serious and potentially life-threatening reactions if used with certain other medicines. See “What is the most important information I should know about EMSAM?”
- may worsen your depression, give you suicidal thoughts, or cause unusual changes in behavior. Call your doctor right away if you feel worse with EMSAM.
- may cause a mental condition called mania or hypomania (mental condition which causes high moods) in people who have a history of mania.
- can cause low blood pressure. Lie down if you feel dizzy, faint, or lightheaded. Change your position slowly if low blood pressure is a problem for you. Tell your doctor if you have these symptoms. You may need a lower dose of EMSAM.

The most common side effect of EMSAM is a skin reaction where the patch is placed. You may see mild redness at the site when a patch is removed. This redness should go away within several hours after removing the patch. If irritation or itching continues, tell your doctor.

These are not all the side effects of EMSAM. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store EMSAM?

- Store EMSAM at 20° to 25° C (68° to 77° F).
- Store EMSAM in its sealed pouch until use.
- Keep EMSAM and all medicines out of the reach of children and away from pets.

General information about EMSAM

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not give EMSAM to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about EMSAM. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about EMSAM that is written for health professionals.

For more information, call 1-866-367-2678 or visit www.EMSAM.com

What are the ingredients in EMSAM?

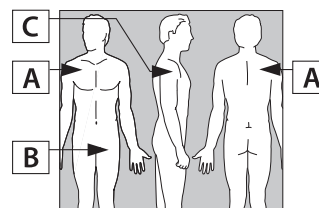
Active Ingredient: Selegiline

Inactive Ingredients: acrylic adhesive, ethylene vinyl acetate, polyethylene, polyester, polyurethane, and silicone coated polyester

How to Use and Apply an EMSAM Patch

Read these instructions carefully before you apply EMSAM (selegiline transdermal system). Ask your doctor or pharmacist about anything you do not understand.

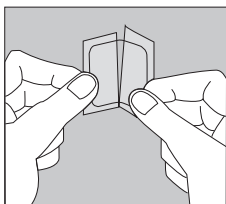
- Apply a new EMSAM patch every day (24 hours).
- Wear only one EMSAM patch at a time. Wear one EMSAM patch all the time until it is time to apply a new one.
- Remove a used patch before applying a new one.
- Change the patch at the same time each day.
- Apply an EMSAM patch to dry, smooth skin on your (A) upper chest or back (below the neck and above the waist), (B) upper thigh, or (C) to the outer surface of the upper arm. Choose a new site each time you change your patch. Do not use the same site 2 days in a row. (See Picture 1 for skin sites that may be used.)



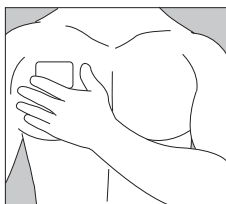
Picture 1. Skin sites for EMSAM patch. (Do not use more than one patch at a time.)

- Apply an EMSAM patch to an area of skin that is not hairy, oily, irritated, broken, scarred, or calloused. Do not place the patch where your clothing is tight, which could cause the patch to rub off.
- After you have selected the site for your patch, wash the area gently and well with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.

- Just before you apply the patch, remove it from its sealed pouch. **Do not keep or store the patch outside of the sealed pouch. Never cut an EMSAM patch into smaller pieces to use.**
- Remove half of the protective backing and throw it away. (See Picture 2.) Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers. With your fingertips, press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface. (See Picture 3.)



Picture 2. Removing the protective backing from an EMSAM patch.



Picture 3. Applying an EMSAM patch.

- After you have applied the patch, wash your hands well with soap and water to remove any medicine that may have gotten on them. **Do not touch your eyes until after you have washed your hands.**
- After 24 hours, remove the patch slowly and carefully to avoid damaging the skin. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.
- Throw away the folded patch so that children and pets cannot reach it. This patch still contains some medicine and could harm a child or pet.
- Gently wash the old application site with warm water and a mild soap to remove any sticky material (adhesive) that stays on your skin after removing the patch. A small amount of baby oil may also be used to remove any adhesive. You may need to use a medical adhesive removal pad that you can get from your pharmacist. Alcohol or other dissolving liquids such as nail polish remover may cause skin irritation and should not be used.
- Wash your hands with soap and water.
- If the patch becomes loose, press it back in place. If your **EMSAM** (selegiline transdermal system) patch falls off, apply a new **EMSAM** patch to a new site and resume your normal schedule for changing patches.
- If you forget to change your patch after 24 hours, remove the old patch, put on a new patch in a different area and continue to follow your original schedule.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PERFORMIST Inhalation Solution safely and effectively. See full prescribing information for PERFORMIST Inhalation Solution.

PERFORMIST® (formoterol fumarate) Inhalation Solution

Initial U.S. Approval: 2001

WARNING: ASTHMA-RELATED DEATH

See full prescribing information for complete boxed warning

- Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. (5.1)
- A placebo-controlled study with another long-acting beta₂-adrenergic agonist (salmeterol) showed an increase in asthma-related deaths in patients receiving salmeterol. (5.1)
- The finding of an increased risk of asthma-related death with salmeterol is considered a class effect of LABA, including formoterol, the active ingredient in PERFORMIST. The safety and efficacy of PERFORMIST in patients with asthma have not been established. All LABA including PERFORMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication. (4, 5.1)

INDICATIONS AND USAGE

PERFORMIST Inhalation Solution is a long-acting beta₂-adrenergic agonist (beta₂-agonist) indicated for:

- Long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. (1.1)

Important limitations of use:

- PERFORMIST Inhalation Solution is not indicated to treat acute deteriorations of chronic obstructive pulmonary disease. (1.2, 5.2)
- PERFORMIST Inhalation Solution is not indicated to treat asthma. (1.2)

DOSAGE AND ADMINISTRATION

For oral inhalation only.

- One 20 mcg/2 mL vial every 12 hours (2)
- For use with a standard jet nebulizer (with a facemask or mouthpiece) connected to an air compressor (2)

DOSAGE FORMS AND STRENGTHS

Inhalation Solution (unit dose vial for nebulization); 20 mcg/2 mL solution (3)

CONTRAINDICATIONS

All LABA, including PERFORMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication. (4)

WARNINGS AND PRECAUTIONS

- Do not initiate PERFORMIST Inhalation Solution in acutely deteriorating patients. (5.2)
- Do not use for relief of acute symptoms. Concomitant short-acting beta₂-agonists can be used as needed for acute relief. (5.2)
- Do not exceed the recommended dose. Excessive use of PERFORMIST Inhalation Solution, or use in conjunction with other medications containing long-acting beta₂-agonists, can result in clinically significant cardiovascular effects, and may be fatal. (5.3, 5.5)
- Life-threatening paradoxical bronchospasm can occur. Discontinue PERFORMIST Inhalation Solution immediately. (5.4)
- Use with caution in patients with cardiovascular or convulsive disorders, thyrotoxicosis, or with sensitivity to sympathomimetic drugs. (5.6, 5.7)

ADVERSE REACTIONS

Most common adverse reactions (≥2% and more common than placebo) are diarrhea, nausea, nasopharyngitis, dry mouth, vomiting, dizziness, and insomnia. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Dey Pharma, L.P. at 1-800-429-7751 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Other adrenergic drugs may potentiate effect. Use with caution. (5.3, 7.1)
- Xanthine derivatives, steroids, diuretics, or non-potassium sparing diuretics may potentiate hypokalemia or ECG changes. Use with caution. (5.7, 7.2, 7.3)
- MAO inhibitors, tricyclic antidepressants and drugs that prolong QTc interval may potentiate effect on the cardiovascular system. Use with extreme caution. (7.4)
- Beta-blockers may decrease effectiveness. Use with caution and only when medically necessary. (7.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved Medication Guide.

Revised: 05/2010

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FULL PRESCRIBING INFORMATION

WARNING: ASTHMA-RELATED DEATH

Long-acting beta₂-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta₂-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol, the active ingredient in PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication [see CONTRAINDICATION (4), WARNINGS AND PRECAUTIONS (5.1)].

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of COPD

PERFOROMIST (formoterol fumarate) Inhalation Solution is indicated for the long-term, twice daily (morning and evening) administration in the maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

1.2 Important Limitations of Use

PERFOROMIST Inhalation Solution is not indicated to treat acute deteriorations of chronic obstructive pulmonary disease [see WARNINGS AND PRECAUTIONS (5.2)].

PERFOROMIST Inhalation Solution is not indicated to treat asthma. The safety and effectiveness of PERFOROMIST Inhalation Solution in asthma have not been established.

2 DOSAGE AND ADMINISTRATION

The recommended dose of PERFOROMIST (formoterol fumarate) Inhalation Solution is one 20 mcg unit-dose vial administered twice daily (morning and evening) by nebulization. A total daily dose greater than 40 mcg is not recommended.

PERFOROMIST Inhalation Solution should be administered by the orally inhaled route via a standard jet nebulizer connected to an air compressor. The safety and efficacy of PERFOROMIST Inhalation Solution have been established in clinical trials when administered using the PARI-LC Plus® nebulizer (with a facemask or mouth-piece) and the PRONEB® Ultra compressor. The safety and efficacy of PERFOROMIST Inhalation Solution delivered from non-compressor based nebulizer systems have not been established.

PERFOROMIST Inhalation Solution should always be stored in the foil pouch, and only removed IMMEDIATELY BEFORE USE. Contents of any partially used container should be discarded.

If the recommended maintenance treatment regimen fails to provide the usual response, medical advice should be sought immediately, as this is often a sign of destabilization of COPD. Under these circumstances, the therapeutic regimen should be re-evaluated and additional therapeutic options should be considered.

The drug compatibility (physical and chemical), efficacy, and safety of PERFOROMIST Inhalation Solution when mixed with other drugs in a nebulizer have not been established.

3 DOSAGE FORMS AND STRENGTHS

PERFOROMIST (formoterol fumarate) Inhalation Solution is supplied as a sterile solution for nebulization in low-density polyethylene unit-dose vials. Each vial contains formoterol fumarate dihydrate, USP equivalent to 20 mcg/2 mL of formoterol fumarate.

4 CONTRAINDICATIONS

All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication. [see WARNINGS and PRECAUTIONS (5.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Asthma-Related Deaths [See BOXED WARNING]

Data from a large placebo-controlled study in asthma patients showed that long-acting beta₂-adrenergic agonists may increase the risk of asthma-related death. Data are not available to determine whether the rate of death in patients with COPD is increased by long-acting beta₂-adrenergic agonists.

A 28-week, placebo-controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs. 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death is considered a class effect of the long-acting beta₂-adrenergic agonists, including PERFOROMIST Inhalation Solution. No study adequate to determine whether the rate of asthma related death is increased in patients treated with PERFOROMIST Inhalation Solution has been conducted. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication. [see CONTRAINDICATIONS (4)].

Clinical studies with formoterol fumarate administered as a dry powder inhaler suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

5.2 Deterioration of Disease and Acute Episodes

PERFOROMIST Inhalation Solution should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition. PERFOROMIST Inhalation Solution has not been studied in patients with acutely deteriorating COPD. The use of PERFOROMIST Inhalation Solution in this setting is inappropriate.

PERFOROMIST Inhalation Solution should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. PERFOROMIST Inhalation Solution has not been studied in the relief of acute symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled short-acting beta₂-agonist.

When beginning PERFOROMIST Inhalation Solution, patients who have been taking inhaled, short-acting beta₂-agonists on a regular basis (e.g., four times a day) should be instructed to discontinue the regular use of these drugs and use them only for symptomatic relief of acute respiratory symptoms. When prescribing PERFOROMIST Inhalation Solution, the healthcare provider should also prescribe an inhaled, short-acting beta₂-agonist and instruct the patient how it should be used. Increasing inhaled beta₂-agonist use is a signal of deteriorating disease for which prompt medical attention is indicated. COPD may deteriorate acutely over a period of hours or chronically over several days or longer. If PERFOROMIST Inhalation Solution no longer controls the symptoms of bronchoconstriction, or the patient's inhaled, short-acting beta₂-agonist becomes less effective or the patient needs more inhalation of short-acting beta₂-agonist than usual, these may be markers of deterioration of disease. In this setting, a re-evaluation of the patient and the COPD treatment regimen should be undertaken at once. Increasing the daily dosage of PERFOROMIST Inhalation Solution beyond the recommended 20 mcg twice daily dose is not appropriate in this situation.

5.3 Excessive Use and Use with Other Long-Acting Beta₂-Agonists

As with other inhaled beta₂-adrenergic drugs, PERFOROMIST Inhalation Solution should not be used more often, at higher doses than recommended, or in conjunction with other medications containing long-acting beta₂-agonists, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

5.4 Paradoxical Bronchospasm

As with other inhaled beta₂-agonists, PERFOROMIST Inhalation Solution can produce paradoxical bronchospasm that may be life-threatening. If paradoxical bronchospasm occurs, PERFOROMIST Inhalation Solution should be discontinued immediately and alternative therapy instituted.

5.5 Cardiovascular Effects

PERFOROMIST Inhalation Solution, like other beta₂-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic and/or diastolic blood pressure, and/or symptoms. If such effects occur, PERFOROMIST Inhalation Solution may need to be discontinued. In addition, beta-agonists have been reported to produce ECG changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Therefore, PERFOROMIST Inhalation Solution, like other sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.6 Coexisting Conditions

PERFOROMIST Inhalation Solution, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to sympathomimetic amines. Doses of the related beta₂-agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.7 Hypokalemia and Hyperglycemia

Beta-agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects [see *CLINICAL PHARMACOLOGY (12.2)*]. The decrease in serum potassium is usually transient, not requiring supplementation. Beta-agonist medications may produce transient hyperglycemia in some patients.

Clinically significant changes in serum potassium and blood glucose were infrequent during clinical studies with long-term administration of PERFOROMIST Inhalation Solution at the recommended dose.

6 ADVERSE REACTIONS

Long acting beta₂-adrenergic agonists such as formoterol increase the risk of asthma-related death [See *BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)*].

6.1 Beta₂-Agonist Adverse Reaction Profile

Adverse reactions to PERFOROMIST Inhalation Solution are expected to be similar in nature to other beta₂-adrenergic receptor agonists including: angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, dry mouth, muscle cramps, palpitations, nausea, dizziness, fatigue, malaise, insomnia, hypokalemia, hyperglycemia, and metabolic acidosis.

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults with COPD

The data described below reflect exposure to PERFOROMIST Inhalation Solution 20 mcg twice daily by oral inhalation in 586 patients, including 232 exposed for 6 months and 155 exposed for at least 1 year. PERFOROMIST Inhalation Solution was studied in a 12-week, placebo- and active-controlled trial (123 subjects treated with PERFOROMIST Inhalation Solution) and a 52-week, active-controlled trial (463 subjects treated with PERFOROMIST Inhalation Solution). Patients were mostly Caucasians (88%) between 40-90 years old (mean, 64 years old) and had COPD, with a mean FEV₁ of 1.33 L. Patients with significant concurrent cardiac and other medical diseases were excluded from the trials.

Table 1 shows adverse reactions from the 12-week, double-blind, placebo-controlled trial where the frequency was greater than or equal to 2% in the PERFOROMIST Inhalation Solution group and where the rate in the PERFOROMIST Inhalation Solution group exceeded the rate in the placebo group. In this trial, the frequency of patients experiencing cardiovascular adverse events was 4.1% for PERFOROMIST Inhalation Solution and 4.4% for placebo. There were no frequently occurring specific cardiovascular adverse events for PERFOROMIST Inhalation Solution (frequency greater than or equal to 1% and greater than placebo). The rate of COPD exacerbations was 4.1% for PERFOROMIST Inhalation Solution and 7.9% for placebo.

Adverse Reaction	PERFOROMIST Inhalation Solution 20 mcg		Placebo	
	n	(%)	n	(%)
Total Patients	123	(100)	114	(100)
Diarrhea	6	(4.9)	4	(3.5)
Nausea	6	(4.9)	3	(2.6)
Nasopharyngitis	4	(3.3)	2	(1.8)
Dry Mouth	4	(3.3)	2	(1.8)
Vomiting	3	(2.4)	2	(1.8)
Dizziness	3	(2.4)	1	(0.9)
Insomnia	3	(2.4)	0	(0)

Patients treated with PERFOROMIST Inhalation Solution 20 mcg twice daily in the 52-week open-label trial did not experience an increase in specific clinically significant adverse events above the number expected based on the medical condition and age of the patients.

7 DRUG INTERACTIONS

7.1 Adrenergic Drugs

If additional adrenergic drugs are to be administered by any route, they should be used with caution because the sympathetic effects of formoterol may be potentiated [see *WARNINGS AND PRECAUTIONS (5.3, 5.5, 5.6, 5.7)*].

7.2 Xanthine Derivatives, Steroids, or Diuretics

Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists [see *WARNINGS AND PRECAUTIONS (5.7)*].

7.3 Non-potassium Sparing Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics.

7.4 MAO Inhibitors, Tricyclic Antidepressants, QTc Prolonging Drugs

Formoterol, as with other beta₂-agonists, should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because the effect of adrenergic agonists on the cardiovascular system may be potentiated by these agents. Drugs that are known to prolong the QTc interval have an increased risk of ventricular arrhythmias.

7.5 Beta-blockers

Beta-adrenergic receptor antagonists (beta-blockers) and formoterol may inhibit the effect of each other when administered concurrently. Beta-blockers not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in COPD patients. Therefore, patients with COPD should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-blockers in patients with COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

Formoterol fumarate administered throughout organogenesis did not cause malformations in rats or rabbits following oral administration. However, formoterol fumarate was found to be teratogenic in rats and rabbits in other testing laboratories. When given to rats throughout organogenesis, oral doses of 0.2 mg/kg (approximately 40 times the maximum recommended daily inhalation dose in humans on a mg/m² basis) and above delayed ossification of the fetus, and doses of 6 mg/kg (approximately 1200 times the maximum recommended daily inhalation dose in humans on a mg/m² basis) and above decreased fetal weight. Formoterol fumarate has been shown to cause stillbirth and neonatal mortality at oral doses of 6 mg/kg and above in rats receiving the drug during the late stage of pregnancy. These effects, however, were not produced at a dose of 0.2 mg/kg. Because there are no adequate and well-controlled studies in pregnant women, PERFOROMIST Inhalation Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Women should be advised to contact their physician if they become pregnant while taking PERFOROMIST Inhalation Solution.

8.2 Labor and Delivery

There are no adequate and well-controlled human studies that have investigated the effects of PERFOROMIST Inhalation Solution during labor and delivery.

Because beta-agonists may potentially interfere with uterine contractility, PERFOROMIST Inhalation Solution should be used during labor only if the potential benefit justifies the potential risk.

8.3 Nursing Mothers

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk, but because many drugs are excreted in human milk, caution should be exercised if PERFOROMIST Inhalation Solution is administered to nursing women. There are no well-controlled human studies of the use of PERFOROMIST Inhalation Solution in nursing mothers.

Women should be advised to contact their physician if they are nursing while taking PERFOROMIST Inhalation Solution.

8.4 Pediatric Use

PERFOROMIST Inhalation Solution is not indicated for use in children. The safety and effectiveness of PERFOROMIST Inhalation Solution in pediatric patients have not been established. The pharmacokinetics of formoterol fumarate has not been studied in pediatric patients.

8.5 Geriatric Use

Of the 586 subjects who received PERFOROMIST Inhalation Solution in clinical studies, 284 were 65 years and over, while 89 were 75 years and over. Of the 123 subjects who received PERFOROMIST Inhalation Solution in the 12-week safety and efficacy trial, 48 (39%) were 65 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of PERFOROMIST Inhalation Solution has not been studied in elderly subjects.

10 OVERDOSAGE

The expected signs and symptoms with overdosage of PERFOROMIST Inhalation Solution are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms listed under ADVERSE REACTIONS. Signs and symptoms may include angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, and metabolic acidosis. As with all inhaled sympathomimetic medications, cardiac arrest and even death may be associated with an overdose of PERFOROMIST Inhalation Solution.

Treatment of overdosage consists of discontinuation of PERFOROMIST Inhalation Solution together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of PERFOROMIST Inhalation Solution. Cardiac monitoring is recommended in cases of overdosage.

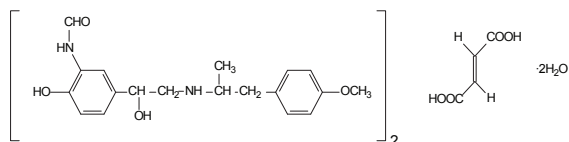
The minimum lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 32,000 times the maximum recommended daily inhalation dose in humans on a mg/m² basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the maximum recommended daily inhalation dose in humans.

For additional information about overdose treatment, call a poison control center (1-800-222-1222).

11 DESCRIPTION

PERFOROMIST (formoterol fumarate) Inhalation Solution is supplied as 2 mL of formoterol fumarate inhalation solution packaged in a 2.5 mL single-use low-density polyethylene vial and overwrapped in a foil pouch. Each vial contains 2 mL of a clear, colorless solution composed of formoterol fumarate dihydrate, USP equivalent to 20 mcg of formoterol fumarate in an isotonic, sterile aqueous solution containing sodium chloride, pH adjusted to 5.0 with citric acid and sodium citrate.

The active component of PERFOROMIST Inhalation Solution is formoterol fumarate dihydrate, USP, a racemate. Formoterol fumarate dihydrate is a beta₂-adrenergic bronchodilator. Its chemical name is (±)-2-hydroxy-5-[(1RS)-1-hydroxy-2-[[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl-amino]ethyl]]formanilide fumarate dihydrate; its structural formula is:



Formoterol fumarate dihydrate, USP has a molecular weight of 840.92 and its empirical formula is (C₁₉H₂₄N₂O₄)₂•C₄H₄O₄•2H₂O. Formoterol fumarate dihydrate, USP is a white to yellowish crystalline powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether.

PERFOROMIST Inhalation Solution does not require dilution prior to administration by nebulization. Like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors and the nebulization system used and its performance.

Using the PARI-LC Plus[®] nebulizer (with a facemask or mouthpiece) connected to a PRONEB[®] Ultra compressor under in vitro conditions, the mean delivered dose from the mouthpiece was approximately 7.3 mcg (37% of label claim). The mean nebulizer flow rate was 4 LPM and the nebulization time was 9 minutes. PERFOROMIST Inhalation Solution should be administered from a standard jet nebulizer at adequate flow rates via a facemask or mouthpiece.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Formoterol fumarate is a long-acting, beta₂-adrenergic receptor agonist (beta₂-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at beta₂-receptors than at beta₁-receptors. Although beta₂-receptors are the predominant adrenergic receptors in bronchial smooth muscle and beta₁-receptors are the predominant receptors in the heart, there are also beta₂-receptors in the human heart comprising 10% to 50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective beta₂-agonists may have cardiac effects.

The pharmacologic effects of beta₂-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenylyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyperresponsiveness. The relevance of these in vitro and animal findings to humans with COPD is unknown.

12.2 Pharmacodynamics

Systemic Safety and Pharmacokinetic / Pharmacodynamic Relationships

The major adverse effects of inhaled beta₂-agonists occur as a result of excessive activation of the systemic beta-adrenergic receptors. The most common adverse effects in adults include skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose.

Changes in serum potassium and serum glucose were evaluated in 12 COPD patients following inhalation of single doses of PERFOROMIST Inhalation Solution containing 10, 20 and 244 mcg of formoterol fumarate (calculated on an anhydrous basis) in a crossover study. At 1 hour after treatment with formoterol fumarate inhalation solution, mean (± standard deviation) serum glucose rose 26 ± 30, 29 ± 28, and 38 ± 44 mg/dL, respectively, and was not significantly different from baseline or trough level at 24 hours post-dose. At 1 hour after dosing with formoterol fumarate inhalation solution 244 mcg, serum potassium fell by 0.68 ± 0.4 mEq/L, and was not different from baseline or trough level at 24 hours post-dose.

Linear pharmacokinetic/pharmacodynamic (PK/PD) relationships between urinary formoterol excretion and decreases in serum potassium, increases in plasma glucose, and increases in heart rate were generally observed with another inhalation formulation of formoterol fumarate and hence would be expected with PERFOROMIST Inhalation Solution also. Following single dose administration of 10-fold the recommended clinical dose of the other formoterol fumarate inhalation formulation having comparable exposure to single dose of 244 mcg of PERFOROMIST Inhalation Solution (approximately 12-fold the recommended clinical dose) in healthy subjects, the formoterol plasma concentration was found to be highly correlated with the reduction in plasma potassium concentration. Data from this study showed that maximum reductions from baseline in plasma potassium ranged from 0.55 to 1.52 mmol/L with a median maximum reduction of 1.01 mmol/L. Generally, the maximum

effect on plasma potassium was noted 1 to 3 hours after peak formoterol plasma concentrations were achieved.

Electrophysiology

In the dose-ranging study of PERFORMIST Inhalation Solution, ECG-determined heart rate increased by a mean of 6 ±3 beats per minute at 6 hours after a single dose of 244 mcg, but was back to predose level at 16-24 hours.

The effect of PERFORMIST Inhalation Solution on heart rate and cardiac rhythm was studied in a 12-week clinical trial comparing PERFORMIST Inhalation Solution to placebo and an active control treatment. COPD patients, including 105 patients exposed to PERFORMIST Inhalation Solution, underwent continuous electrocardiographic (Holter) monitoring during two 24-hour periods (study baseline and after 8-12 weeks of treatment). ECGs were performed pre-dose and at 2 to 3 hours post-dose at study baseline (prior to dosing) and after 4, 8 and 12 weeks of treatment. Bazett's and Fridericia's methods were used to correct the QT interval for heart rate (QTcB and QTcF, respectively). The mean increase from baseline in QTcB interval over the 12-week treatment period was ≤ 4.8 msec for PERFORMIST Inhalation Solution and ≤ 4.6 msec for placebo. The percent of patients who experienced a maximum change in QTc greater than 60 msec at any time during the 12-week treatment period was 0% and 1.8% for PERFORMIST Inhalation Solution and placebo, respectively, based on Bazett's correction, and 1.6% and 0.9%, respectively, based on Fridericia's correction. Prolonged QT was reported as an adverse event in 1 (0.8%) patient treated with PERFORMIST Inhalation Solution and 2 (1.8%) placebo patients. No occurrences of atrial fibrillation or ventricular tachycardia were observed during 24-hour Holter monitoring or reported as adverse events in patients treated with PERFORMIST Inhalation Solution after the start of dosing. No increase in supraventricular tachycardia over placebo-treated subjects was observed. The mean increase in maximum heart rate from baseline to 8-12 weeks after the start of dosing was 0.6 beats per minute (bpm) for patients treated with PERFORMIST Inhalation Solution twice daily compared to 1.2 bpm for placebo patients. There were no clinically meaningful differences from placebo in acute or chronic effects on heart rate, including QTcB and QTcF, or cardiac rhythm resulting from treatment with PERFORMIST Inhalation Solution.

At an exposure from formoterol fumarate dry powder formulation comparable to approximately 12-fold the recommended dose of PERFORMIST Inhalation Solution, a mean maximum increase of pulse rate of 26 bpm was observed 6 hours post dose in healthy subjects. This study showed that the maximum increase of mean corrected QT interval (QTc) was 25 msec when calculated using Bazett's correction and was 8 msec when calculated using Fridericia's correction. The QTc returned to baseline within 12 to 24 hours post-dose. Formoterol plasma concentrations were weakly correlated with pulse rate and increase of QTc duration. The effects on pulse rate and QTc interval are known pharmacological effects of this class of study drug and were not unexpected at this supratherapeutic formoterol fumarate inhalation dose.

Tachyphylaxis / Tolerance

Tolerance to the effects of inhaled beta-agonists can occur with regularly-scheduled, chronic use. In a placebo-controlled clinical trial in 351 adult patients with COPD, the bronchodilating effect of PERFORMIST Inhalation Solution was determined by the FEV₁ area under the curve over 12 hours following dosing on Day 1 and after 12 weeks of treatment. The effect of PERFORMIST Inhalation Solution did not decrease after 12 weeks of twice-daily treatment (Figures 1 and 2).

12.3 Pharmacokinetics

Information on the pharmacokinetics of formoterol (dry powder and/or inhalation solution) in plasma and/or urine is available in healthy subjects as well as patients with chronic obstructive pulmonary disease after oral inhalation of doses at and above the therapeutic dose.

Urinary excretion of unchanged formoterol was used as an indirect measure of systemic exposure. Plasma drug disposition data parallel urinary excretion, and the elimination half-lives calculated for urine and plasma are similar.

Absorption

Pharmacokinetic properties of formoterol fumarate were evaluated in 12 COPD patients following inhalation of single doses of PERFORMIST Inhalation Solution containing 10, 20 and 244 mcg of formoterol fumarate (calculated on an anhydrous basis) and 12 mcg formoterol fumarate dry powder, through 36 hours after single-dose administration. Formoterol fumarate concentrations in plasma following the 10 and 20 mcg doses of PERFORMIST Inhalation Solution and the 12 mcg dose of

formoterol fumarate dry powder were undetectable or only detected sporadically at very low concentrations. Following a single 244 mcg dose of PERFORMIST Inhalation Solution (approximately 12 times the recommended clinical dose), formoterol fumarate concentrations were readily measurable in plasma, exhibiting rapid absorption into plasma, and reaching a maximum drug concentration of 72 pg/mL within approximately 12 minutes of dosing.

The mean amount of formoterol excreted unchanged in 24 hour urine following single oral inhalation doses of 10, 20, and 244 mcg PERFORMIST Inhalation Solution were found to be 109.7 ng, 349.6 ng, and 3317.5 ng, respectively. These findings indicate a near dose proportional increase in systemic exposure within the dose range tested.

When 12 mcg of a dry powder formulation of formoterol fumarate was given twice daily to COPD patients by oral inhalation for 12 weeks, the accumulation index, based on the urinary excretion of unchanged formoterol was 1.19 to 1.38. This suggests some accumulation of formoterol in plasma with multiple dosing. Although multiple-dose pharmacokinetic data is unavailable from PERFORMIST Inhalation Solution, assumption of linear pharmacokinetics allows a reasonable prediction of minimal accumulation based on single-dose pharmacokinetics. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol fumarate delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

The binding of formoterol to human plasma proteins *in vitro* was 61% to 64% at concentrations from 0.1 to 100 ng/mL. Binding to human serum albumin *in vitro* was 31% to 38% over a range of 5 to 500 ng/mL. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 244 mcg dose of PERFORMIST Inhalation Solution.

Metabolism

Formoterol is metabolized primarily by direct glucuronidation at either the phenolic or aliphatic hydroxyl group and O-demethylation followed by glucuronide conjugation at either phenolic hydroxyl groups. Minor pathways involve sulfate conjugation of formoterol and deformylation followed by sulfate conjugation. The most prominent pathway involves direct conjugation at the phenolic hydroxyl group. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2'-hydroxyl group. *In vitro* studies showed that multiple drug-metabolizing enzymes catalyze glucuronidation (UGT1A1, 1A8, 1A9, 2B7 and 2B15 were the most predominant enzymes) and O-demethylation (CYP2D6, CYP2C19, CYP2C9 and CYP2A6) of formoterol. Formoterol did not inhibit CYP450 enzymes at therapeutically relevant concentrations. Some patients may be deficient in CYP2D6 or 2C19 or both. Whether a deficiency in one or both of these isozymes results in elevated systemic exposure to formoterol or systemic adverse effects has not been adequately explored.

Excretion

Following administration of single 10, 20, and 244 mcg PERFORMIST Inhalation Solution doses (calculated on an anhydrous basis) delivered via nebulizer in 12 COPD patients, on average, about 1.1% to 1.7% of the dose was excreted in the urine as unchanged formoterol as compared to about 3.4% excreted unchanged following inhalation administration of 12 mcg of formoterol fumarate dry powder. Renal clearance of formoterol following inhalation administration of PERFORMIST Inhalation Solution in these subjects was about 157 mL/min. Based on plasma concentrations measured following the 244 mcg dose, the mean terminal elimination half-life was determined to be 7 hours.

Gender

As reported for another formoterol fumarate inhalation formulation, upon correction for body weight, pharmacokinetics of formoterol fumarate did not differ significantly between males and females.

Geriatric, Pediatric, Hepatic/Renal Impairment

The pharmacokinetics of formoterol fumarate has not been studied in elderly and pediatric patient populations. The pharmacokinetics of formoterol fumarate has not been studied in subjects with hepatic or renal impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of formoterol fumarate has been evaluated in 2-year

drinking water and dietary studies in both rats and mice. In rats, the incidence of ovarian leiomyomas was increased at doses of 15 mg/kg and above in the drinking water study and at 20 mg/kg in the dietary study (AUC exposure approximately 2300 times human exposure at the maximum recommended daily inhalation dose), but not at dietary doses up to 5 mg/kg (AUC exposure approximately 570 times human exposure at the maximum recommended daily inhalation dose). In the dietary study, the incidence of benign ovarian theca-cell tumors was increased at doses of 0.5 mg/kg (AUC exposure was approximately 57 times human exposure at the maximum recommended daily inhalation dose) and above. This finding was not observed in the drinking water study, nor was it seen in mice (see below).

In mice, the incidence of adrenal subcapsular adenomas and carcinomas was increased in males at doses of 69 mg/kg (AUC exposure approximately 1000 times human exposure at the maximum recommended daily inhalation dose) and above in the drinking water study, but not at doses up to 50 mg/kg (AUC exposure approximately 750 times human exposure at the maximum recommended daily inhalation dose) in the dietary study. The incidence of hepatocarcinomas was increased in the dietary study at doses of 20 and 50 mg/kg in females (AUC exposures approximately 300 and 750 times human exposure at the maximum recommended daily inhalation dose, respectively) and 50 mg/kg in males, but not at doses up to 5 mg/kg (AUC exposure approximately 75 times human exposure at the maximum recommended daily inhalation dose). Also in the dietary study, the incidence of uterine leiomyomas and leiomyosarcomas was increased at doses of 2 mg/kg (AUC exposure was approximately 30 times human exposure at the maximum recommended daily inhalation dose) and above. Increases in leiomyomas of the rodent female genital tract have been similarly demonstrated with other beta-agonist drugs.

Formoterol fumarate was not mutagenic or clastogenic in the following tests: mutagenicity tests in bacterial and mammalian cells, chromosomal analyses in mammalian cells, unscheduled DNA synthesis repair tests in rat hepatocytes and human fibroblasts, transformation assay in mammalian fibroblasts and micronucleus tests in mice and rats.

Reproduction studies in rats revealed no impairment of fertility at oral doses up to 3 mg/kg (approximately 600 times the maximum recommended daily inhalation powder dose in humans on a mg/m² basis).

13.2 Animal Pharmacology

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown. [See *DRUG INTERACTIONS, Xanthine Derivatives, Steroids, or Diuretics (7.2)*]

14 CLINICAL STUDIES

14.1 Adult COPD Trial

PERFOROMIST (formoterol fumarate) Inhalation Solution was evaluated in a 12-week, double-blind, placebo- and active-controlled, randomized, parallel-group, multicenter trial conducted in the United States. Of a total enrollment of 351 adults (age range: 40 to 86 years; mean age: 63 years) with COPD who had a mean pre-bronchodilator FEV₁ of 1.34 liters (44% of predicted), 237 patients were randomized to PERFOROMIST Inhalation Solution 20 mcg or placebo, administered twice daily via a PARI-LC Plus[®] nebulizer with a PRONEB[®] Ultra compressor. The diagnosis of COPD was based upon a prior clinical diagnosis of COPD, a smoking history (at least 10 pack-years), age (at least 40 years), and spirometry results (pre-bronchodilator baseline FEV₁ at least 30% and less than 70% of the predicted value, and the FEV₁/FVC less than 70%). About 58% of patients had bronchodilator reversibility, defined as a 10% or greater increase in FEV₁ after inhalation of 2 actuations (180 mcg) of albuterol from a metered dose inhaler. About 86% (106) of patients treated with PERFOROMIST Inhalation Solution and 74% (84) of placebo patients completed the trial.

PERFOROMIST Inhalation Solution 20 mcg twice daily resulted in significantly greater post-dose bronchodilation (as measured by serial FEV₁ for 12 hours post-dose; the primary efficacy analysis) compared to placebo when evaluated at endpoint (week 12 for completers and last observation for dropouts). Similar results were seen on Day 1 and at subsequent timepoints during the trial.

Mean FEV₁ measurements at Day 1 (Figure 1) and at endpoint (Figure 2) are shown below.

Figure 1
Mean* FEV₁ at Day 1

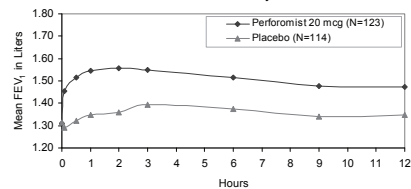
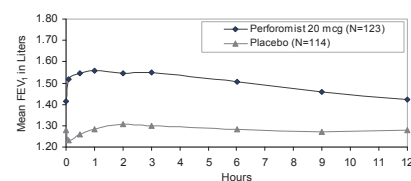


Figure 2
Mean* FEV₁ at Endpoint after 12 Weeks of Treatment



*Figures show least-squares means adjusted for baseline FEV₁

Patients treated with PERFOROMIST Inhalation Solution used less rescue albuterol during the trial compared to patients treated with placebo.

Examination of age (≥65 or younger) and gender subgroups did not identify differences in response to PERFOROMIST Inhalation Solution. There were too few non-Caucasian subjects to assess differences in populations defined by race adequately.

In the 12 week study, 78% of subjects achieved a 15% increase from baseline FEV₁ following the first dose of PERFOROMIST Inhalation Solution 20 mcg. In these subjects, the median time to onset of bronchodilation, defined as 15% increase in FEV₁, was 11.7 minutes. When defined as an increase in FEV₁ of 12% and 200 mL, the time to onset of bronchodilation was 13.1 minutes after dosing. The median time to peak bronchodilator effect was 2 hours after dosing.

16 HOW SUPPLIED/STORAGE AND HANDLING

PERFOROMIST (formoterol fumarate) Inhalation Solution is supplied as a 2 mL sterile solution for nebulization in 2.5 mL low-density polyethylene unit dose vials. Each vial is overwrapped in a foil pouch and supplied in cartons as listed below.

Carton of 60 individually wrapped unit dose vials, NDC 49502-605-61

Storage and Handling:

Prior to dispensing to the patient: Store in a refrigerator, 2°C to 8°C (36°F to 46°F)

After dispensing to the patient: Store at 2°C to 25°C (36°F to 77°F) for up to 3 months. Protect pouch from heat.

- PERFOROMIST Inhalation Solution should only be administered via a standard jet nebulizer connected to an air compressor with an adequate airflow and equipped with a facemask or mouthpiece.
- Vial should always be stored in the foil pouch, and only removed IMMEDIATELY before use.
- Do not take by mouth.
- Contents of any partially used container should be discarded.
- Discard the container and top after use.
- Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Asthma-Related Death

Patients should be informed that long acting beta agonist, such as PERFOROMIST, increase the risk of asthma-related death. All LABA, including PERFOROMIST, should not be used in patients with asthma without use of a long-term asthma control medication.

Acute Exacerbations or Deteriorations

PERFOROMIST Inhalation Solution is not indicated for relief of acute symptoms, and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta₂-agonist (the healthcare provider should provide the patient with such medication and instruct the patient in how it should be used). Patients should be instructed to seek medical attention if their symptoms worsen despite recommended doses of PERFOROMIST Inhalation Solution, if PERFOROMIST Inhalation Solution treatment becomes less effective, or if they need more inhalations of a short-acting beta₂-agonist than usual.

Appropriate Dosing

Patients should not stop using PERFOROMIST Inhalation Solution unless told to do so by a healthcare provider because symptoms may get worse. Patients should not inhale more than the prescribed number of vials at any one time. The daily dosage of PERFOROMIST Inhalation Solution should not exceed one vial twice daily (40 mcg total daily dose). Excessive use of sympathomimetics may cause significant cardiovascular effects, and may be fatal.

Concomitant Therapy

Patients who have been taking inhaled, short-acting beta₂-agonists (e.g., albuterol) on a regular basis should be instructed to discontinue the regular use of these products and use them only for symptomatic relief of acute symptoms. PERFOROMIST Inhalation Solution should not be used in conjunction with other inhaled medications containing long-acting beta₂-agonists. Patients should be warned not to stop or change the dose of other concomitant COPD therapy without medical advice, even if symptoms improve after initiating treatment with PERFOROMIST Inhalation Solution.

Common Adverse Reactions with Beta₂-agonists

Patients should be informed that treatment with beta₂-agonists may lead to adverse reactions that include palpitations, chest pain, rapid heart rate, increased or decreased blood pressure, headache, tremor, nervousness, dry mouth, muscle cramps, nausea, dizziness, fatigue, malaise, low blood potassium, high blood sugar, high blood acid, or trouble sleeping [see ADVERSE REACTIONS (6.1)].

Instructions for Administration

It is important that patients understand how to use PERFOROMIST Inhalation Solution with a nebulizer appropriately [see the accompanying Medication Guide]. Patients should be instructed not to mix other medications with PERFOROMIST Inhalation Solution or ingest PERFOROMIST Inhalation Solution. Patients should throw the plastic dispensing container away immediately after use. Due to their small size, the container and top pose a danger of choking to young children.

FDA-Approved Medication Guide

See the accompanying Medication Guide.



DEY Pharma, L.P., Napa, CA 94558

U.S. Pat. No. 6,667,344

U.S. Pat. No. 6,814,953

03-848-03D

MEDICATION GUIDE

PERFOROMIST® (Per-FOR-o-mist) (formoterol fumarate) Inhalation Solution

PERFOROMIST Inhalation Solution is only for use with a nebulizer.

Read the Medication Guide that comes with PERFOROMIST Inhalation Solution before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about PERFOROMIST Inhalation Solution?

PERFOROMIST Inhalation Solution can cause serious side effects including:

- **People with asthma who take long-acting beta₂ adrenergic agonist (LABA) medicines such as PERFOROMIST Inhalation Solution have an increased risk of death from asthma problems.**
- It is not known if LABA medicines, such as PERFOROMIST Inhalation Solution, increase the risk of death in people with chronic obstructive pulmonary disease (COPD).
- **Get emergency medical care if:**
 - **breathing problems worsen quickly**
 - **you use your rescue inhaler medicine, but it does not relieve your breathing problems**

What is PERFOROMIST Inhalation Solution?

PERFOROMIST Inhalation Solution is used long term, 2 times a day (morning and evening), in controlling symptoms of chronic obstructive pulmonary disease (COPD) in adults with COPD.

PERFOROMIST Inhalation Solution is only for use with a nebulizer. LABA medicines such as PERFOROMIST Inhalation Solution help the muscles around the airways in your lungs stay relaxed to prevent symptoms, such as wheezing, cough, chest tightness, and shortness of breath.

PERFOROMIST Inhalation Solution is not for use to treat sudden symptoms of COPD.

PERFOROMIST Inhalation Solution should not be used in children. It is not known if PERFOROMIST Inhalation Solution is safe and effective in children.

It is not known if PERFOROMIST Inhalation Solution is safe and effective in people with asthma.

Who should not use PERFOROMIST Inhalation Solution?

Do not use PERFOROMIST Inhalation Solution if you have asthma without using a long-term asthma control medicine.

What should I tell my healthcare provider before using PERFOROMIST Inhalation Solution?

Tell your healthcare provider about all of your health conditions, including if you:

- **have heart problems**
- **have high blood pressure**
- **have diabetes**
- **have seizures**
- **have thyroid problems**
- **have liver problems**
- **are pregnant or planning to become pregnant.** It is not known if PERFOROMIST Inhalation Solution can harm an unborn baby.
- **are breastfeeding.** It is not known if PERFOROMIST Inhalation Solution passes into breast milk and if it can harm your baby.

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. PERFOROMIST Inhalation Solution and certain other medicines may interact with each other. This may cause serious side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist each time you get a new medicine.

How should I use PERFOROMIST Inhalation Solution?

Read the step-by-step instructions for using PERFOROMIST Inhalation Solution at the end of this Medication Guide.

- Use PERFOROMIST Inhalation Solution exactly as prescribed. One ready-to-use vial of PERFOROMIST Inhalation Solution is one dose. The usual dose of PERFOROMIST Inhalation Solution is one ready-to-use vial, twice a day (morning and evening) breathed in through your nebulizer machine. The 2 doses should be about 12 hours apart. **Do not use more than 2 vials of PERFOROMIST Inhalation Solution a day.**
- Do not mix other medicines with PERFOROMIST Inhalation Solution in your nebulizer machine.
- If you miss a dose of PERFOROMIST Inhalation Solution, just skip that dose. Take your next dose at your usual time. Do not take 2 doses at one time.
- While you are using PERFOROMIST Inhalation Solution 2 times each day:
 - **do not use** other medicines that contain a long-acting beta₂-agonist (LABA) for any reason.
 - **do not use** your short-acting beta₂-agonist medicine on a regular basis (four times a day).
- **PERFOROMIST Inhalation Solution does not relieve sudden symptoms of COPD.** Always have a rescue inhaler medicine with you to treat sudden symptoms. If you do not have a rescue inhaler medicine, call your healthcare provider to have one prescribed for you.
- Do not stop using **PERFOROMIST Inhalation Solution** or other medicines to control or treat your COPD unless told to do so by your healthcare provider because your symptoms might get worse. Your healthcare provider will change your medicines as needed.
- **Do not use PERFOROMIST Inhalation Solution:**
 - **more often than prescribed,**
 - **more medicine than prescribed for you, or**
 - **with other LABA medicines**

Call your healthcare provider or get emergency medical care right away if:

- your breathing problems worsen with PERFOROMIST Inhalation Solution
- you need to use your rescue inhaler medicine more often than usual
- your rescue inhaler medicine does not work as well for you at relieving symptoms

What are the possible side effects of PERFOROMIST Inhalation Solution?

PERFOROMIST Inhalation Solution can cause serious side effects, including:

- See "What is the most important information I should know about PERFOROMIST Inhalation Solution?"
- **Sudden shortness of breath immediately after use of PERFOROMIST Inhalation Solution.**
- **Serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue, and breathing problems.** Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.
- **chest pain**
- **increased or decreased blood pressure**
- **a fast and irregular heartbeat**
- **low blood potassium**
- **high blood sugar**
- **high blood acid**

Common side effects of PERFOROMIST Inhalation Solution include:

- **headache**
- **tremor**
- **nervousness**
- **dry mouth**

- muscle cramps
- nausea, vomiting
- diarrhea
- dizziness
- tiredness
- trouble sleeping
- If your COPD symptoms worsen over time do not increase your dose of PERFOROMIST Inhalation Solution, instead call your healthcare provider.

Tell your healthcare provider if you get any side effect that bothers you or that does not go away.

These are not all the side effects with PERFOROMIST Inhalation Solution. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PERFOROMIST Inhalation Solution?

- Store PERFOROMIST Inhalation Solution in a refrigerator between 36° to 46°F (2° to 8°C) in the protective foil pouch. Protect from light and heat. **Do not open a sealed pouch until you are ready to use a dose of PERFOROMIST Inhalation Solution. Once a sealed pouch is opened, PERFOROMIST Inhalation Solution must be used right away.** PERFOROMIST Inhalation Solution may be used directly from the refrigerator.
- PERFOROMIST Inhalation Solution may also be stored at room temperature between 68°F to 77°F (20°C to 25°C) for up to 3 months (90 days). If stored at room temperature, discard PERFOROMIST Inhalation Solution if it is not used after 3 months or if past the expiration date, whichever is sooner. Space is provided on the packaging to record dispense date and use by date.
- Do not use PERFOROMIST Inhalation Solution after the expiration date provided on the foil pouch and vial.
- PERFOROMIST Inhalation Solution should be colorless. Discard PERFOROMIST Inhalation Solution if it is not colorless.
- **Keep PERFOROMIST Inhalation Solution and all medicines out of the reach of children.**

General Information about PERFOROMIST Inhalation Solution

Medicines are sometimes prescribed for purposes that are not mentioned in a Medication Guide. Do not use PERFOROMIST Inhalation Solution for a condition for which it was not prescribed. Do not give PERFOROMIST Inhalation Solution to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about PERFOROMIST Inhalation Solution. If you would like more information, talk with your health care provider. You can ask your health care provider or pharmacist for information about PERFOROMIST Inhalation Solution that was written for healthcare professionals.

- For customer service, call 1-800-395-3376
- To report side effects, call 1-877-446-3679
- For medical information, call 1-800-429-7751

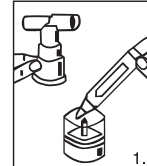
Instructions for Using PERFOROMIST (formoterol fumarate) Inhalation Solution

PERFOROMIST Inhalation Solution is used only in a standard jet nebulizer machine connected to an air compressor. Make sure you know how to use your nebulizer machine before you use it to breathe in PERFOROMIST Inhalation Solution or other medicines.

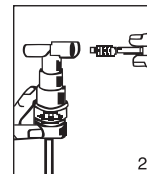
Do not mix PERFOROMIST Inhalation Solution with other medicines in your nebulizer machine.

PERFOROMIST Inhalation Solution comes sealed in a foil pouch. Do not open a sealed pouch until you are ready to use a dose of PERFOROMIST Inhalation Solution.

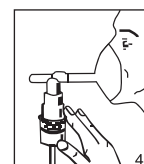
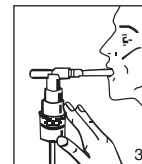
1. Remove vial from the foil pouch.
2. Twist the cap completely off the vial and squeeze all the medicine into the nebulizer medicine cup (reservoir) (FIGURE 1).



3. Connect the nebulizer reservoir to the mouthpiece or facemask (FIGURE 2).



4. Connect the nebulizer to the compressor.
5. Sit in a comfortable, upright position. Place the mouthpiece in your mouth (FIGURE 3) or put on the facemask (FIGURE 4); and turn on the compressor.



6. Breathe as calmly, deeply and evenly as possible through your mouth until no more mist is formed in the nebulizer reservoir. The average nebulization time is 9 minutes. At this point, the treatment is finished.
7. Discard the PERFOROMIST Inhalation Solution container and top after use.
8. Clean the nebulizer (see manufacturer's instructions).



DEY Pharma, L.P.
Napa, CA 94558 U.S.A.

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This Medication Guide has been approved by the U.S. Food and Drug Administration

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