EMSAM®
Selegiline Transdermal System

NDA 21,336/21,708

Psychopharmacologic Drugs Advisory Committee
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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1 EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) issued an approvable letter on January 31, 2004, noting that the safety and efficacy of Somerset's New Drug Applications (NDAs) for the acute and maintenance treatment of major depressive disorder (MDD) had been established. Three placebo-controlled trials support the efficacy of EMSAM® (selegiline transdermal system) - one short-term trial at a 20 mg fixed dose, one short-term trial at doses of 20-40 mg, and one long-term trial at a 20 mg fixed dose.

EMSAM 20, 30, and 40 mg is a transdermal, daily-administered antidepressant. Selegiline (the drug substance of EMSAM) is an irreversible inhibitor of monoamine oxidase (MAO). When applied, EMSAM is designed to deliver selegiline continuously over a 24-hour period.

The purpose of this document is to demonstrate that EMSAM 20 mg can be safely administered without dietary modifications. The rationale supporting this recommendation includes the following:

- The tyramine challenge model showed that the tyramine sensitivity of EMSAM 20 mg was pharmacodynamically equivalent to that of oral selegiline (Eldepryl® 10 mg/day, a monoamine oxidase inhibitor [MAOI] approved without dietary modifications and indicated for Parkinson's disease), and was 20-fold better than tranylcypromine (Parnate® 30 mg/day, a [MAOI approved without dietary modifications and indicated for MDD).
- A food challenge pharmacodynamic test showed that people cannot eat sufficient quantities of tyramine-rich foods to pose a safety concern with EMSAM 20 mg.
- Oral selegiline 10 mg/day has been safely administered to patients with Parkinson's disease for 16 years without dietary modifications.
- EMSAM (20-40 mg), in the clinical program, has been safely administered to 2,503 patients with MDD (820 patient years) without dietary modifications and with no reports of hypertensive crisis.

Based upon the data from the clinical program, Somerset proposes labeling to reflect that EMSAM 20 mg can be safely administered without dietary modifications. In order to convey effectively the dietary modifications needed for EMSAM 30 and 40 mg, dosing instructions are clearly defined throughout the Physician Labeling, Patient Leaflet, and packaging.

2 INTRODUCTION

2.1 Background

Despite the wide availability of clinically efficacious treatments for depression, as many as 50% of patients who initiate treatment do not respond, and as many as 30% do not benefit from a series of treatment trials (Thase, 2004). Available pharmacotherapy for MDD is based on the observation that agents that increase monoamine transmission (norepinephrine [NE] and serotonin [5HT]) are effective antidepressants. Since the 1980s, the general direction of pharmacotherapy has been toward increasing specificity. The selective serotonin reuptake inhibitors (SSRIs) supplanted the tricyclic antidepressants (TCAs) as the treatment of choice by targeting a single neurotransmitter (5HT). SSRIs are better tolerated than TCAs with respect to cardiovascular and anticholinergic side effects. Despite this advancement, greater efficacy with these newer agents has not been observed compared to the older agents, and side effects, including sexual dysfunction, have limited patients' adherence to medication therapy and have reduced their quality of life (Cassano and Fava, 2004; Montgomery et al., 2005).

Efficacy with MAOIs was first observed in the early 1950s, and these agents soon became the mainstay of pharmacological treatment for depression. During subsequent decades, the efficacy of MAOIs for the acute and maintenance treatment of MDD was established. MAOIs were temporarily removed from the market, however, due to the occurrence of hypertensive crises associated with dietary tyramine and the inhibition of MAO in the gastrointestinal (GI) and hepatic systems. MAOIs were later reintroduced into the market with dietary tyramine modifications. Due to the requirement of following a tyramine-modified diet while taking these drugs, however, MAOI use dwindled, and they are currently underutilized (Robinson, 2002).

MAOIs are a heterogeneous class of drugs that share the ability to block oxidative deamination of the naturally-occurring monoamines: dopamine, 5HT, NE, epinephrine, and phenylethylamine. They exert their therapeutic effect by inhibiting MAO in the brain. They also can inhibit intestinal and hepatic MAO activity, which raises dietary concerns, because one function of intestinal and hepatic MAO enzymes is to serve as an effective barrier against systemic absorption of dietary tyramine. In the presence of sufficient GI tract MAO inhibition, the physiological intestinal tyramine barrier is compromised, and

dietary tyramine can be absorbed systemically, potentially causing a sympathetic neuron-mediated acute hypertensive crisis known as a "cheese reaction" because of its association with the intake of certain cheeses (Blackwell et al., 1967).

2.2 The Development of EMSAM

The development of EMSAM as an antidepressant grew out of the interest in providing an MAOI antidepressant that would permit effective dosing without dietary tyramine complications.

Selegiline, or R-(-)-N, 2-dimethyl-N-2-propynylphenylamine, was first discovered in 1965, and is classified as a selective, irreversible MAOI (Mahmood, 1997; Knoll, 1983). Selegiline HCl in an oral form is available both in the US and Europe for use in patients with Parkinson's disease (Standaert and Young, 2001). At the recommended total dose of 10 mg/day, no dietary modifications are required, and selegiline is a selective inhibitor of MAO-B (Chrisp et al., 1991).

MAO is a flavin-containing enzyme that is widely distributed throughout the body, with high activity concentrated in the liver, kidneys, intestinal wall, and brain. It exists as 2 isoenzymes: type A (MAO-A) and type B (MAO-B). MAO-A is the predominant form in the intestinal mucosa, while the MAO-B isoenzyme is predominant in the central nervous system (thalamus, striatum, cortex, and brainstem). Only MAO-A is present within the peripheral neuron. MAO-A preferentially deaminates NE and 5HT, while MAO-B preferentially deaminates phenylethylamine. Tyramine and dopamine are common substrates for both isoenzymes.

The literature suggests the necessity for MAO-A inhibition within brain tissue for antidepressant activity with MAOIs. Selective MAO-B inhibition is observed at the recommended oral doses of 10 mg/day of selegiline for Parkinson's disease. At higher doses, this selectivity is lost, and MAO-A is also inhibited (Prasad et al., 1988; Schulz et al., 1989; Sunderland et al., 1985). This finding first led to the investigation of the antidepressant potential of selegiline.

Published data from 6 controlled trials with oral selegiline HCl demonstrated efficacy in the dose range of 30-60 mg (Sunderland et al., 1994; McGrath et al., 1989; Mann et al., 1982, 1989; Mendlewicz and Youdim, 1978, 1983; Mendis et al., 1981; Quitkin et al.,

1984; Mann and Gershon, 1987; Sabelli, 1991; Birkmayer et al., 1984). At these higher doses, inhibition of intestinal and hepatic MAO-A becomes significant, and dietary tyramine modification is necessary. This diminishes the potential clinical utility of oral selegiline HCl in the treatment of depression.

EMSAM was developed with pharmacokinetic (PK) and pharmacodynamic properties in order to overcome the safety risks associated with higher oral selegiline doses and dietary tyramine. By delivering systemic drug through the skin rather than through intestinal absorption, EMSAM permits achievement of higher brain MAO inhibition relative to GI MAO inhibition. At therapeutic doses, this formulation permits an antidepressant effect while maintaining the integrity of the intestinal and hepatic MAO-A barrier to ingested amines (Barrett et al., 1996). To support this assertion, Somerset conducted animal studies demonstrating that transdermal administration of selegiline provides high sustained plasma concentrations of selegiline with preferential inhibition of MAO-B and MAO-A in brain tissue while preserving activity of MAO-A in peripheral organs (Somerset Pharmaceuticals, Inc. nonclinical study Pharm 19; Mawhinney et al., 2003). This is demonstrated by contrasting the pharmacodynamic effects of oral selegiline vs. transdermal selegiline on different tissues. In a guinea pig model, at steady-state, oral and transdermal selegiline doses cause high (and presumed antidepressant) levels of MAO-A inhibition in cortex and striatum. In marked contrast, while oral selegiline also produces significant MAO-A inhibition in the duodenum and liver (Figure 1) clear separation is observed with EMSAM with regards to MAO inhibition between brain and gastrointestinal tract tissues (Figure 2).

Figure 1. Effect of Oral Selegiline at Steady State on MAO-A Inhibition

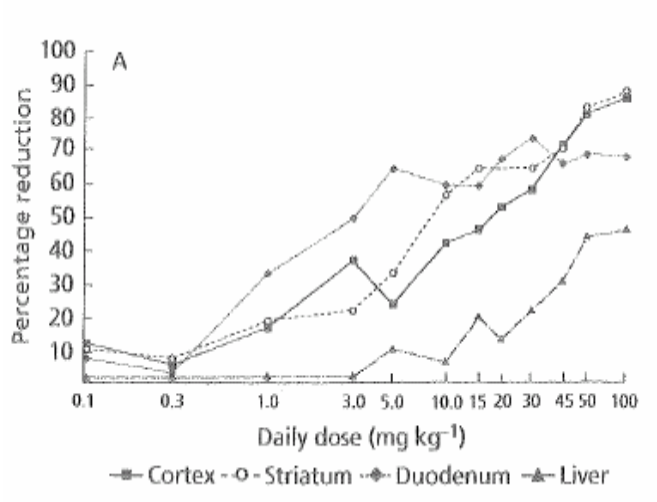
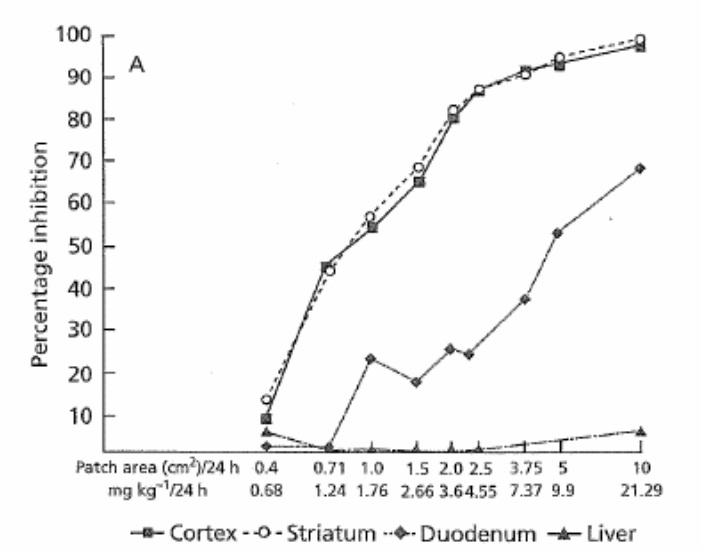


Figure 2. Effect of EMSAM at Steady State on MAO-A Inhibition



Even at the highest observed EMSAM-induced brain MAO-A inhibition, hepatic MAO-A function (and presumed tyramine-metabolizing capacity) remained robust, presumably due to portal-epithelial MAOI containing cells receiving most of their blood supply from portal vein blood draining from the intestines rather than from the systemic portal artery supply. Similar evidence of preferential brain inhibition of MAOI vs. GI system inhibition of MAOI was demonstrated in rats as well (Wecker et al., 2003).

3 PROGRAM SUMMARY

3.1 Overview of Biopharmaceutics / Pharmacokinetics

The biopharmaceutics/PK program consisted of > 30 studies examining dermally applied doses of 5-40 mg selegiline in > 650 subjects. Single- and multiple-dose studies were conducted to establish the PK profile in volunteers, as well as in geriatric, pediatric, hepatically-impaired, renally-impaired, and depressed patients. The potential for drug interactions was also studied. The metabolism of selegiline was defined in *in vitro* and *in vivo* studies. The principal findings of the program are discussed below.

3.1.1 Drug Delivery Profile

- Approximately 25%–30% of the selegiline in EMSAM was delivered within 24 hours.
    - EMSAM 20 mg delivered approximately 6 mg/24 hours of selegiline.
    - EMSAM 30 and 40 mg delivered approximately 9 and 12 mg/24 hours of selegiline, respectively.
- There was a linear relationship between applied and delivered dose.
- Selegiline plasma concentration varied approximately 25%-30% from the mean. Overlap in the plasma concentrations of selegiline was observed for adjacent doses (20 mg vs. 30 mg, 30 mg vs. 40 mg) of EMSAM.

3.1.2 Absorption, Bioavailability and Dose Proportionality

- EMSAM was extensively absorbed, with plasma levels being maintained over a 24-hour period, allowing a once-daily application.
- Steady-state plasma levels of selegiline are reached after 5 days of treatment.
- Transdermally administered selegiline produced higher, more sustained steady-state levels than orally administered selegiline, but reduced the levels of metabolites formed. The bioavailability was 75% following EMSAM treatment and 4.4% after oral administration due to the first-pass metabolism (see Appendix 1).
- Dose proportionality during treatment with EMSAM across the therapeutic range occurred with the delivered selegiline dose.

3.1.3 Protein-binding, Distribution, Metabolism and Drug-Drug Interactions

- Selegiline was 89% to 92% bound to plasma proteins.

- Selegiline was rapidly distributed throughout the body and quickly penetrated the central nervous system.
- Metabolism was the major elimination route for selegiline.
    - Cross species comparisons demonstrated that selegiline was metabolized either via N-dealkylation or N-depropargylation.
    - Selegiline was metabolized by multiple CYP_{P450} isoenzymes. The isoenzymes included CYP2C9, 2B6, 3A4, and 2A6A (minor role).
    - No relevant PK or pharmacodynamic drug-drug interactions were observed between selegiline and alprazolam, risperidone, olanzapine, ibuprofen, warfarin, levothyroxine, alcohol (ethanol), ketoconazole, pseudoephedrine, phenylpropanolamine, or carbamazepine during EMSAM treatment.
- Dose adjustments were not necessary with EMSAM in specific populations:
    - Patients with various stages of renal or hepatic failure treated with EMSAM 20 mg demonstrated similar PK properties to other healthy volunteers.
    - Population PK analysis of the Phase 3 MDD patients exposed to EMSAM demonstrated that apparent plasma clearance of selegiline was independent of dose, age, gender, race, renal function, body weight, or concomitant medications taken.

3.2 Extent of Exposure

3.2.1 Clinical Trials in Major Depressive Disorder (MDD)

It is noteworthy that dietary modifications were removed from Somerset's clinical program after discussion with the FDA regarding the clinically supportive results of a tyramine-rich food challenge study. This study was designed to provoke a potential sudden increase in blood pressure after EMSAM-treated subjects ingested abnormally large quantities of tyramine-rich aged cheeses. Although encouraged to eat as much cheese as possible, subjects who had been administered EMSAM 20 mg for 14 days could not eat enough to cause a significant increase in blood pressure. With the exception of the first clinical trial (S9303-E106, N=153), all patients in the MDD trials were treated without dietary modifications.

Safety population data were last submitted to the FDA in July 2003, and consisted of data from 2036 patients with MDD exposed to EMSAM (Table 1). For this pool of patients, the mean time on study medication was 92.6 days, and the median time on medication was 70 days.

Since the latest complete submission to the FDA, an additional 620 patients with MDD were exposed to EMSAM (Table 1). For these additional patients, the mean time on study medication was 170.7 days, and the median time was 115 days.

Of the 2656 patients treated with EMSAM, 1093 received treatment for at least 3 months, and 514 received treatment for at least 6 months. Of these patients, 211 received treatment for ≥ 12 months. Out of the 1093 patients that received EMSAM for at least 90 days, 140 were elderly patients (≥ 65 years of age) and 953 were non-elderly (< 65 years of age).

An additional 17 patients with MDD were enrolled in a compassionate-use study (S9303-P0043), and were exposed to EMSAM 20 mg for a minimum of < 1 month to a maximum of up to 34 months.

Table 1. EMSAM Exposure in Patients with MDD[a]

	EMSAM 10 mg	**EMSAM 20 mg**	**EMSAM 30/40 mg[b]**	**Total**
N	**103**	**1576**	**357**	**2036**
Mean duration (days)	44.8	90.4	116.0	92.6
Median duration (days)	55.0	70.0	110.0	70.0
Range (days)	5 – 66	1 – 473	1 – 427	1 – 473
Additional exposure since submission (study S9303-P0204)				
N	**n/a**	**30**	**590**	**620**
Mean duration (days)	n/a	14.8	178.6	170.7
Median duration (days)	n/a	7.5	117.5	115.0
Range (days)	n/a	2 – 172	8 – 403	2 – 403
Total N	**103**	**1606**	**947**	**2656[c]**
Cumulative exposure data				
Min. 3 mos. on EMSAM (n)	0	489	604	1093
Min. 6 mos. on EMSAM (n)	0	194	320	514
Min. 12 mos. on EMSAM (n)	0	43	168	211

[a] All patients with the exception of those participating in study S9303-E106-96B of EMSAM 20 mg (N=153) were treated without dietary modifications.
[b] Includes exposure to EMSAM 20 mg during titration phase.
[c] Patients who received at least 1 dose of EMSAM 20 mg.
MDD = major depressive disorder and n/a = not applicable.

July 2003 submission to FDA

3.3 Efficacy

On January 31, 2004, the FDA issued an approvable letter noting that the safety and efficacy of Somerset's NDAs for the acute and maintenance treatment of MDD had been established.

The efficacy of EMSAM as a treatment for MDD was established in 2 placebo-controlled studies of 6 and 8 weeks duration in adult outpatients (aged 18 to 70 years) meeting Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) criteria for MDD (Table 2). In both studies, patients were randomized to double-blind treatment with EMSAM or placebo. The 6-week trial (N=176) showed that fixed-dose EMSAM 20 mg was significantly more effective than placebo on the 17-item Hamilton Depression Rating Scale (HAM-D). Similar results were noted for the secondary efficacy endpoints: 28-item HAM-D score, Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impression-Severity Scale (CGI-s) and Clinical Global Impression of Change (CGI-c). The 8-week dose-titration trial (N=265) showed that EMSAM at a starting dose of 20 mg, with possible increases to 30 or 40 mg based on clinical response, showed significant improvement compared with placebo on the primary outcome measure, the 28-item HAM-D score, and the secondary outcome measures, including MADRS, CGI-s, and CGI-c.

In a longer-term trial, 322 patients meeting DSM-IV criteria for MDD who had responded during an initial 10-week open-label treatment phase with fixed-dose EMSAM 20 mg were randomized to continuation of EMSAM, at the same dose, or to placebo, for up to 52 weeks of observation for relapse (Table 2). 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. Relapse during the double-blind phase was defined as: (1) a 17-item HAM-D score ≥ 14, (2) a CGI-s score of ≥ 3 (with at least a 2-point increase from double-blind baseline), and (3) meeting DSM-IV criteria for MDD on 2 consecutive visits ≥ 11 days apart. Patients receiving continued EMSAM experienced a significantly longer time to relapse over the subsequent 52 weeks compared to those receiving placebo.

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

Table 2. EMSAM Pivotal Trials Supporting the NDA

	S9303-E106-96B	**S9303-P0052**[+]	**S9303-P9806**[+]
Duration	6 weeks	8 weeks	52 weeks
N	176	265	322
Age (Mean, Range)	42, 20-65	42, 18-70	43, 18-81
Dose	EMSAM 20 mg vs. Placebo	EMSAM 20 to 40 mg vs. Placebo	EMSAM 20 mg vs. Placebo
Primary Endpoint	$HAM\text{-}D_{1\text{-}17}$ p = 0.018	$HAM\text{-}D_{1\text{-}28}$ p = 0.033	K-M Relapse[*] p = 0.006

[+] Patients in these studies followed a normal diet.
[*] K-M Relapse = Kaplan-Meier time to relapse analysis.
$HAM\text{-}D_{1\text{-}17}$ = 17-item Hamilton Depression Rating Scale and NDA = New Drug Application.

3.4 General Clinical Safety

During the MDD clinical development program, 2,503 patients (820 patient years) were safely exposed to EMSAM 20-40 mg without dietary modifications. EMSAM was generally well tolerated, and of particular note, weight changes and levels of sexual dysfunction were similar among EMSAM- and placebo-treated patients (see Appendices 2A and 2B). There were no clinical meaningful changes in blood pressure between the EMSAM and placebo groups, nor were there any apparent trends in the vital signs over time except for the highest EMSAM dose group (30 or 40 mg), which had a decrease from baseline in resting and standing systolic blood pressure (SBP) of -4.5 mm Hg and -6.0 mm Hg, respectively, at end of study.

Adverse events (AEs) during exposure were obtained primarily by general inquiry and recorded by clinical investigators. Standard Coding Symbols for a Thesaurus of Adverse Reactions Terms (COSTART) terminology was used to classify reported AEs (Table 3). The stated frequencies of AEs represent the proportion of individuals who experienced at least one treatment-emergent AE 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.

The most common AE was application site reactions, and all of these events were mild or moderate in severity and generally did not require further treatment. (Patients receiving EMSAM will be instructed to change application sites daily to reduce the risk of such a reaction.)

Table 3. Incidence of the Most Common Treatment-emergent Adverse Events in Placebo-controlled Clinical Trials of MDD

COSTART 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

Note: Events reported by at least 2% of patients treated with EMSAM are included, except for the following events that had an incidence on placebo treatment $\geq$ to EMSAM: infection, nausea, dizziness, pain, abdominal pain, nervousness, back pain, asthenia, anxiety, flu syndrome, accidental injury, somnolence, rhinitis, and palpitations.
COSTART = Coding Symbols for a Thesaurus of Adverse Reactions Terms and MDD = major depressive disorder.

4 TYRAMINE

Somerset conducted a clinical pharmacology program to explore the cardiovascular safety of the concomitant administration of EMSAM with tyramine. This program

consisted of 14 trials with a total of 214 subjects who were challenged multiple times with oral encapsulated tyramine, both before and after treatment with EMSAM (see Table 4, Section 4.2 below). Tyramine sensitivity was studied with respect to the following variables and comparators: a) time of exposure (10, 21, 30, 60, 90, and 96 days), b) dose (20, 30, and 40 mg EMSAM), c) fasting versus fed conditions, and d) comparator drugs (oral selegiline, tranylcypromine, and fluoxetine).

4.1 Pressor Response to Tyramine

Oral MAOI antidepressants have long been associated with a risk of tyramine-induced hypertensive crisis. Dietary tyramine represents the predominant source of plasma tyramine. Hypertension induced by dietary tyramine in patients taking oral MAOIs is known as the "cheese effect" because some aged cheeses have a relatively high mg/g content of tyramine, and because the majority of documented cases of tyramine-induced hypertension were related to these cheeses. In contrast to largely held myths about the extent of food and beverages that contain excessive amounts of tyramine (e.g., all cheeses, alcoholic beverages), only a few contain amounts of tyramine large enough to be practically important (e.g., fermented sausage, air-dried meat, yeast extract [Marmite®], specific aged cheeses, some soy products, and some imported tap beers) (Blackwell et al., 1967; Folks, 1983; McCabe, 1986; Shulman et al., 1989).

Although most single meals contain little, if any, tyramine (Shulman et al., 1989; Gardner et al., 1996; Shulman and Walker, 1999), a hypothetical tyramine–rich meal could contain as much as 40 mg of tyramine. Normally, the ingestion of tyramine-rich food is without cardiovascular effect, since 3 enzymatic barriers are available to metabolize and inactivate tyramine at the level of the intestine, liver, and adrenergic neuron.

When administered systemically, the cardiovascular actions of tyramine mimic NE actions, which include vascular constriction and an increase in cardiac rate and contractile force (Hoffman and Lefkowitz, 1990). Each of these actions occurs simultaneously in a dose-related fashion. However, tyramine has a very short (< 1 hour) PK and pharmacodynamic half-life (Dollery et al., 1983; Huebert et al., 1994; VanDenBerg et. al., 2003), which limits the duration of these reactions. Given a sufficient bolus tyramine, however, the resulting hypertension (referred to as the tyramine pressor response) can be severe, resulting in a hypertensive crisis that forms the basis of the

contraindications to dietary tyramine associated with available oral MAOI antidepressants.

When an inhibitor of MAO-A is administered orally, the inactivation of GI and hepatic MAO-A prevents the metabolism of tyramine in the intestinal mucosa and liver. This inhibition of tyramine metabolism permits absorption of tyramine into the circulation, and therefore, into adrenergic nerve terminals causing release of NE, potentially causing a hypertensive event. It is therefore apparent that an agent such as selegiline would be without the "cheese effect," if administered at a dose and route that could maximize MAO inhibition in the brain and minimize MAO inhibition in the intestinal tract.

4.2 Tyramine Pressor Test Model

Somerset assessed the potential for this cardiovascular interaction between EMSAM and dietary tyramine using the tyramine pressor test (also referred to as a tyramine challenge) in a series of studies with healthy volunteers in a controlled and monitored in-patient environment. Such challenges are the standard method of assessment of vulnerability to dietary tyramine. These tests involve monitoring the SBP and heart rate of normal volunteers in response to tyramine administration before and after dosing with EMSAM or other test agents. A sustained rise in SBP of ≥ 30 mm Hg above baseline (hypertensive event) was considered the endpoint, and SBP responses > 60 mm Hg above baseline were generally terminated by administering labetalol, an adrenoceptor-blocking agent. Because the endpoint of the challenge was ***not*** a hypertensive crisis, rather a 30 mm Hg increase, this challenge was not a measure of the rate of hypertensive crises associated with a treatment regimen. Rather, it was an experimentally-controlled, safe, objective measure of the physiological tyramine defensive barrier. (A hypertensive crisis, by contrast, can be defined as a critical elevation in blood pressure [>180/120 mm Hg] leading to end-organ damage in the central nervous system, heart, or kidneys [Chobanian et al., 2000].)

This model permitted comparisons of dietary tyramine tolerance and metabolism among different drugs and different drug formulations (i.e., oral versus transdermal delivery of selegiline). The model also allowed assessment of the timing of reaching pharmacodynamic steady-state of maximum tyramine sensitivity to EMSAM (approximately 30 days in humans) and assessment of the impact of co-administration of

tyramine with food (i.e., 2 to 3 times more tyramine was required when consumed as food to induce the same hypertensive response compared with the fasting condition; see Section 4.3.4 below).

The enzymatic barriers to tyramine in unmedicated physiological states are quite effective. On average, an untreated person requires a dose of approximately 500 mg of encapsulated tyramine, administered in a fasting state, in order to produce a pressor response (defined as an increase in SBP of ≥ 30 mm Hg above baseline). By contrast, a person treated with a non-selective oral MAOI, such as tranylcypromine (Parnate), would have a similar response after approximately 10 mg of encapsulated tyramine (in a fasted state) or 25 mg in a fed state, signifying that a hypertensive crisis might occur following the ingestion of a tyramine-rich meal containing 40 mg of tyramine. Studies have shown an association between tranylcypromine and hypertensive crisis following ingestion of a tyramine-rich meal (Blackwell et al., 1967). Thus, there is a qualitative relationship between a low pressor dose and hypertensive crisis among patients exposed to tranylcypromine.

The food study demonstrated that it was physically impossible to ingest enough high tyramine content food to provoke a hypertensive response in subjects receiving EMSAM 20 mg. In order to deliver the substantial amounts of tyramine needed to produce an endpoint response (i.e., a sustained rise in SBP of ≥ 30 mm Hg above baseline) in untreated and treated subjects, an encapsulated form of tyramine powder was administered with water. Dosing in the Somerset tyramine challenge studies with encapsulated tyramine thereby produced a bolus effect that was an extreme challenge of cardiovascular physiology and highly unlikely to have been encountered during a normal meal. Moreover, in most of the Somerset tyramine sensitivity studies, capsules were administered to subjects who had fasted for at least 8 hours prior to the challenge. These test conditions maximized systemic absorption of tyramine, and accordingly, most of the tyramine sensitivity data presented below represents an “extreme case” that delivered a rate and amount of tyramine exposure that far surpasses what could be achieved in non-laboratory dining conditions.

Somerset also investigated the differences observed in pressor doses obtained in fasted versus fed states in study S9303-P0201. This fed study was performed both to a) substantiate the previously published data that showed the margin of safety to tyramine

exposure in fed subjects was 2- to 3-fold greater than in fasting subjects (Korn et al., 1988a, 1988b; Berlin et al., 1989), and b) to validate the previously published PK assessment that systemic exposure to a tyramine dose (area under the concentration-time curve [AUC]) was reduced by > 50%, and maximum plasma concentration (Cmax) was reduced by > 70% when administered with food rather than fasting(study S9303-P0157; VanDenBerg et al., 2003). Additionally, the time to tyramine maximum plasma concentration was delayed when oral tyramine was administered with food.

Two hundred and fourteen healthy subjects (including 31 subjects > 50 years of age) completed a series of tyramine challenge studies employing a similar experimental design (Table 4). Studies were conducted to explore the effect of applied doses of EMSAM 20 to 40 mg and length of treatment of EMSAM (up to 96 days) on the cardiovascular safety of concomitant orally consumed tyramine. In addition, the change in cardiovascular sensitivity to tyramine was compared among treatments with EMSAM 20 mg and oral selegiline HCl (5 mg twice daily [b.i.d.]), tranylcypromine (an irreversible, non-selective MAOI; 30 mg/day) or fluoxetine (a selective SSRI; 20 mg three times daily). These drugs were chosen for comparison with EMSAM 20 mg because oral selegiline and fluoxetine have been approved in the US and considered safe for clinical use without dietary modifications for the last 16 years, while tranylcypromine requires dietary tyramine modifications.

Table 4. Studies Submitted in the NDA to Support of the Safety of Concomitant Administration of EMSAM with Orally-ingested Tyramine

Study Number	Study Description	Study Drug / Dose	N/n[a]	Exposure[b]
S9303-010-94B	Parallel group study to examine blood pressure response to oral tyramine solution and single application of 1, ½, or ¼ EMSAM	STS (18.4 mg/15 cm^2) STS (9.15 mg/5cm^2) STS (4.6 mg/2.5cm^2)	5/5 5/5 5/5	24 hours
S9303-033-96B*	Parallel group study to evaluate tyramine sensitivity before and during steady-state treatment 15 and 30 mg	STS (15 mg/15 cm^2) STS (30 mg/20 cm^2)	9/8 9/7	21 days
S9303-037-97B*	Study to evaluate tyramine sensitivity before and during steady-state treatment with EMSAM 20 mg	STS (20 mg/20 cm^2)	10/8	21 days
S9303-P9802*	Placebo-controlled study to examine the blood pressure response to food with high tyramine content before and during steady-state treatment with EMSAM 20 mg	STS (20 mg/20 cm^2)	16/12	13 days
S9303-P9816	Study to evaluate the variability and sensitivity to tyramine capsules taken with a standard meal	STS was not administered	4/4	0 days
S9303-P9932*	Study to evaluate tyramine sensitivity before and during steady-state treatment with EMSAM 20 mg	STS (20 mg/20 cm^2)	24/24	9 days
S9303-P9934†	Study to evaluate tyramine sensitivity before and during steady-state treatment with oral Eldepryl®	Oral selegiline HCl 5 mg twice daily	21/21	9 days
S9303-P9940*†	Re-evaluation of subjects from study S9303-P9934 to evaluate tyramine sensitivity before and during steady-state treatment with EMSAM 20 mg	STS (20 mg/20 cm^2)	13/13	9 days
S9303-P9941*†	Crossover study to compare tyramine sensitivity before and after steady-state treatment with EMSAM or Parnate®	STS (20 mg/20 cm^2) Tranylcypromine sulfate 30 mg	12/10	10 days 8 days[c]
S9303-P9942†	Study to evaluate tyramine sensitivity before and during steady-state treatment with Prozac®	Fluoxetine HCl 60 mg (20 mg x 3)	18/12	48 days[d]

Table 4. Studies Submitted in the NDA to Support of the Safety of Concomitant Administration of EMSAM with Orally-ingested Tyramine

Study Number	Study Description	Study Drug / Dose	N/n[a]	Exposure[b]
S9303-P0045*	Study to evaluate tyramine sensitivity before and during steady-state treatment with EMSAM 20 mg	STS (20 mg/20 cm^2)	13/12	33 days
S9303-P0048*	Study to evaluate tyramine sensitivity before and during steady-state treatment with EMSAM 30 mg	STS (30 mg/30 cm^2)	12/10	10 days
S9303-P0050*	Study to evaluate tyramine sensitivity before and during steady-state treatment with EMSAM 40 mg (2 x 20 mg)	STS 2 x (20 mg/20 cm^2)	14/12	10 days
S9303-P0201*	Study to evaluate stability of tyramine sensitivity over time with EMSAM 40 mg	STS (40 mg/40 cm^2)	24/8	93 days

[a] N = Number of subjects that entered study; n=number of subjects that completed.
[b] Exposure time to STS.
[c] Exposure time to tranylcypromine.
[d] Exposure time to fluoxetine (no STS was administered in this study).
* Used to calculate total number of subjects in interaction studies of tyramine with steady-state concentrations of the STS.
† Used to calculate total number of subjects in STS (20 mg/20 cm^2) comparison studies.
NDA = New Drug Application and STS = selegiline transdermal system.

4.3 Tyramine Pressor Results in Fasted State

Results of the fasted tyramine challenge data are summarized in Table 5. The tyramine pressor dose represents the average minimum oral dose of tyramine required to produce an increase in the SBP of ≥ 30 mm Hg above baseline (endpoint). This value was used to calculate the individual subject change in sensitivity to tyramine (TSF value; see below) following treatment with an MAOI agent. The ratio of tyramine pressor doses before (baseline) and after MAOI drug administration provides a relative index of change in cardiovascular sensitivity to tyramine and is referred to as the TSF value. (For example, a patient exhibiting a baseline tyramine pressor dose of 500 mg and an on-treatment tyramine pressor dose of 250 mg would exhibit a TSF of 2.). The TSF values, as well as baseline and on-drug tyramine pressor dose values for the tyramine challenge studies, are presented in Table 5. Note that the non-MAOI fluoxetine (Prozac®) produced a TSF of 1.4.

Table 5. Summary of Tyramine Challenge Results

Study Number	Treatment / Duration	Mean Tyramine Pressor Dose (mg)			TSF Value[c]
		Baseline[a]	Active[b]	Minimum Pressor Dose	
S9303-033-96B	EMSAM 15 mg/ 21 days	625 ± 71	350 ± 93	≥200 mg	1.94 ± 0.68
S9303-P9932	EMSAM 20 mg/ 9 days	495 ± 112	288 ± 108	≥200 mg	1.85 ± 0.51
S9303-P9940	EMSAM 20 mg/ 9 days	550 ± 102	338 ± 112	≥200 mg	1.75 ± 0.54
S9303-037-97B	EMSAM 20 mg/ 21 days	600 ± 0	263 ± 119	≥50 mg	3.56 ± 3.48[d]
S9303-P0045	EMSAM 20 mg/ 33 days	483 ± 139	204 ± 86	≥50 mg	2.85 ± 1.55
S9303-P0048	EMSAM 30 mg/ 10 days	470 ± 148	210 ± 88	≥100 mg	2.40 ± 0.69
S9303-033-96B	EMSAM 30 mg/ 21 days	571 ± 76	107 ± 45	≥50 mg	6.14 ± 2.85
S9303-P0050	EMSAM 40 mg/ 10 days	588 ± 117	198 ± 98	≥75 mg	3.47 ± 1.25
S9303-P9934	Eldepryl® 5 mg twice daily / 9 days	529 ± 115	357 ± 147	≥100 mg	1.70 ± 0.84
S9303-P9941	Parnate® 30 mg/ 8 days	400 ± 71	10 ± 0	≤10 mg	40.0 ± 7.1
	EMSAM 20 mg/ 10 days	480 ± 89	270 ± 82	≥200 mg	1.86 ± 0.42
S9303-P9942	Prozac® 60 mg/ 48 days	533 ± 91	408 ± 131	≥200 mg	1.43 ± 0.56
Pooled analysis[e]	EMSAM 20 mg/ 9-10 days	507 ± 106	298 ± 105	≥200 mg	1.82 ± 0.49

[a] Tyramine pressor dose in fasted state prior to administration of EMSAM or comparison agent.
[b] Tyramine pressor dose in fasted state after steady-state administration of EMSAM or comparison agent.
[c] TSF = tyramine sensitivity factor calculated as the ratio of baseline average pressor dose to the pressor dose during active treatment (mean of individual values).
[d] The higher TSF in this study reflects 1 individual with a TSF of 12 and a 50 mg pressor dose.
[e] Mean results of 47 subjects from studies S9303-P9932, S9303-P9940, and S9303-P9941.

The TSF value corrects for individual (subject-to-subject) differences in baseline sensitivity to tyramine, and may be employed as a true comparative measure of the relative change in the cardiovascular response to tyramine among MAOI agents. For example, a comparison of mean TSF values of tranylcypromine, EMSAM 20 mg, and oral selegiline 5 mg b.i.d. demonstrated that tranylcypromine had a 40-fold increase in cardiovascular sensitivity to tyramine compared to a 1.8-fold increase with EMSAM 20 mg (study S9303-P9941) and 1.7-fold increase with oral selegiline (study S9303-P9934) (Table 6). Comparisons of this type are useful in comparing the change in sensitivity to oral tyramine among agents, and provide an estimate of the relative risk of provoking a hypertensive event following dietary tyramine consumption. The mean TSF values for oral selegiline and EMSAM 20 mg were essentially the same.

Table 6. Crossover Studies with Oral Selegiline and Tranylcypromine

Study Number	Treatment	N	Daily Dose / Duration	Minimum Pressor Dose	TSF Value
S9303-P9934*	Oral Selegiline	13	5 mg b.i.d./9 days	≥ 100 mg	1.67 ± 1.04
S9303-P9940*	EMSAM	13	20 mg/9 days	≥ 200 mg	1.75 ± 0.54
S9303-P9941	Tranylcypromine	10	30 mg/8 days	≤ 10 mg	40.0 ± 7.1
	EMSAM	10	20 mg/10 days	≥ 200 mg	1.86 ± 0.42

* The same subjects were dosed in studies S9303-P9934 and S9303-P9940.
b.i.d. = twice daily and TSF = tyramine sensitivity factor.

4.3.1 Short-term Exposure Data

Short-term exposure data were obtained from 3 different tyramine challenge studies over a 1-year period, and demonstrate the consistency of the results obtained with EMSAM 20 mg. From the data presented in Table 7, it can be seen that fasted subjects that were dosed for 10 consecutive days with EMSAM 20 mg demonstrated only a small increase in sensitivity (TSF ≈ 1.8) to oral tyramine. Because of the physiological barrier against dietary tyramine excess, even a doubling or tripling of tyramine sensitivity is within an acceptable margin of safety, as demonstrated by the on-treatment pressor doses. The mean oral tyramine pressor dose in 47 fasted subjects (pooled analysis) treated with EMSAM 20 mg was 298 ± 105 mg tyramine. All of the subjects in these studies needed

at least 200 mg of encapsulated oral tyramine to reach the endpoint (SBP ≥ 30 mm Hg above baseline on 3 consecutive measures). The individual baseline and on-treatment tyramine pressor doses and the corresponding TSF values for each of the 47 subjects can be found in Appendix 3.

Higher doses of EMSAM were also studied in fasted subjects and compared to EMSAM 20 mg (Table 7). In these studies, an expected dose-dependent, linear increase in sensitivity to tyramine was observed, presumably as a greater level of MAO-A inhibition occurred in intestinal and other peripheral tissue sites. Applied doses of 20, 30, or 40 mg of selegiline via EMSAM for 10 days produced TSF values of 1.8, 2.4, or 3.5, respectively (Table 7; pooled analysis; studies S9303-P0048 and S9303-P0050). Again, each of these values was judged clinically acceptable, since the mean oral tyramine pressor doses obtained following 20, 30, or 40 mg of dermally applied selegiline via EMSAM were 298 ± 105, 210 ± 88, or 198 ± 98 mg of tyramine, respectively, and as all subjects required at least 75 mg of encapsulated oral tyramine while fasting to reach the endpoint (SBP ≥30 mm Hg above baseline on 3 consecutive measures). As noted earlier, 75 mg of encapsulated oral tyramine as delivered in these fasting challenge studies would correspond with doses of 150-225 mg of food-based tyramine.

Table 7. Summary of the Effect of EMSAM Dose on Tyramine Pressor Test (Fasting)

			Mean Tyramine Pressor Dose (mg)			
Study Number	**Daily EMSAM Dose / Duration**	**TSF Ratio[a]**	**Baseline Average**	**Active**	**Difference**	**Minimum Tyramine Pressor Dose[b]**
S9303-P9932	20 mg/9 days	1.85 ± 0.51	495 ± 112	288 ± 108	-208 ± 104	≥ 200 mg
S9303-P9940	20 mg/9 days	1.75 ± 0.54	550 ± 102	338 ± 112	-212 ± 98	≥ 200 mg
S9303-P9941	20 mg/10 days	1.86 ± 0.42	480 ± 89	270 ± 82	-210 ± 70	≥ 200 mg
S9303-P0048	30 mg/10 days	2.40 ± 0.69	470 ± 148	210 ± 88	-260 ± 115	≥ 100 mg
S9303-P0050	40 mg/10 days	3.47 ± 1.25	588 ± 117	198 ± 98	-390 ± 86	≥ 75 mg

[a] TSF = tyramine sensitivity factor calculated as the ratio of baseline average pressor dose to EMSAM interaction pressor dose.
[b] Minimum tyramine pressor dose during EMSAM interaction period.
Note: Tyramine pressor doses are expressed as the free base equivalent.

4.3.2 Extended-term Exposure Data

To define the pharmacodynamic plateau of EMSAM 20 mg, extended-term exposure trials were conducted. Study S9303-P0045 employed the same study design as the short-term studies, with the exception that EMSAM exposure was increased to 33 days. The mean pressor dose was 204 ± 86 mg of tyramine at 33 days versus 298 ± 105 mg of tyramine at 10 days of exposure. The corresponding mean TSF value at 33 days of exposure was 2.85 ± 1.55 compared to 1.82 ± 0.49 at 10 days of exposure.

To test the hypothesis further that pharmacodynamic steady state was reached at about 30 days of treatment with EMSAM, Somerset conducted a study with EMSAM 40 mg that challenged subjects with encapsulated tyramine after 30, 60, and 90 days of treatment. Eighteen subjects completed the initial 30 days of treatment, and 11 subjects completed all phases of the trial up to 90 days of EMSAM 40 mg exposure. The tyramine pressor doses at 30, 60, and 90 days of EMSAM treatment remained consistent. Repeated measures analysis of these data demonstrated no statistical differences among these values ($p > 0.3$). Thus, this study provides supporting data that the pharmacodynamic steady state was achieved for the tyramine pressor dose at ≤ 30 days of EMSAM treatment. Further, these data demonstrate that long-term treatment with EMSAM will not continue to produce a decline in the tyramine pressor dose. Statistical analysis of the TSF values demonstrated similar results (see Table 8).

Table 8. Extended-term Exposure Data – 20 – 40 mg EMSAM (Fasting)

Tyramine Pressor Dose	Dose	N (Subjects)	Mean ± SD (mg tyramine)	Min. (mg tyramine)	Max. (mg tyramine)	TSF Value (Mean ± SD)
S9303-P0045 (33 days)	20	12	204 ± 86	50.0	400.0	2.85 ± 1.55
S9303-P0201 Period 3 (30-day assessment)	40	11	95 ± 76 [a,b]	25.0	200.0	10.99 ± 7.74 [c]
S9303-P0201 Period 4 (60-day assessment)	40	11	72 ± 48 [b]	25.0	200.0	10.58 ± 4.98 [c]
S9303-P0201 Period 5 (90-day assessment)	40	11	88 ± 60 [b]	37.5	200.0	9.32 ± 5.18 [c]

[a] Statistically significant from baseline ($p < 0.0001$; N=11).
[b] Repeated measures analysis on within subject time effect: Periods 3, 4, and 5 ($p > 0.3$; N=11).
[c] Repeated measures analysis on within subject time effect: Periods 3, 4, and 5 ($p > 0.5$; N=11).
N = number of subjects, SD = standard deviation, and TSF = tyramine sensitivity factor.

4.3.3 Pressor Test Model in Comparative Agents (Fasting)

EMSAM 20 mg was also compared to other agents with clinical experience and proven clinical safety. These agents included oral selegiline HCl (5 mg b.i.d.) because the active compound was the same as EMSAM and it had a favorable safety record. Tranylcypromine sulphate (Parnate, 30 mg/day) was chosen because it was in the same drug class, and required dietary tyramine modifications (Blackwell et al., 1967), and fluoxetine HCl, (Prozac, 60 mg/day) was chosen as a negative control (Table 6 and Figure 3).

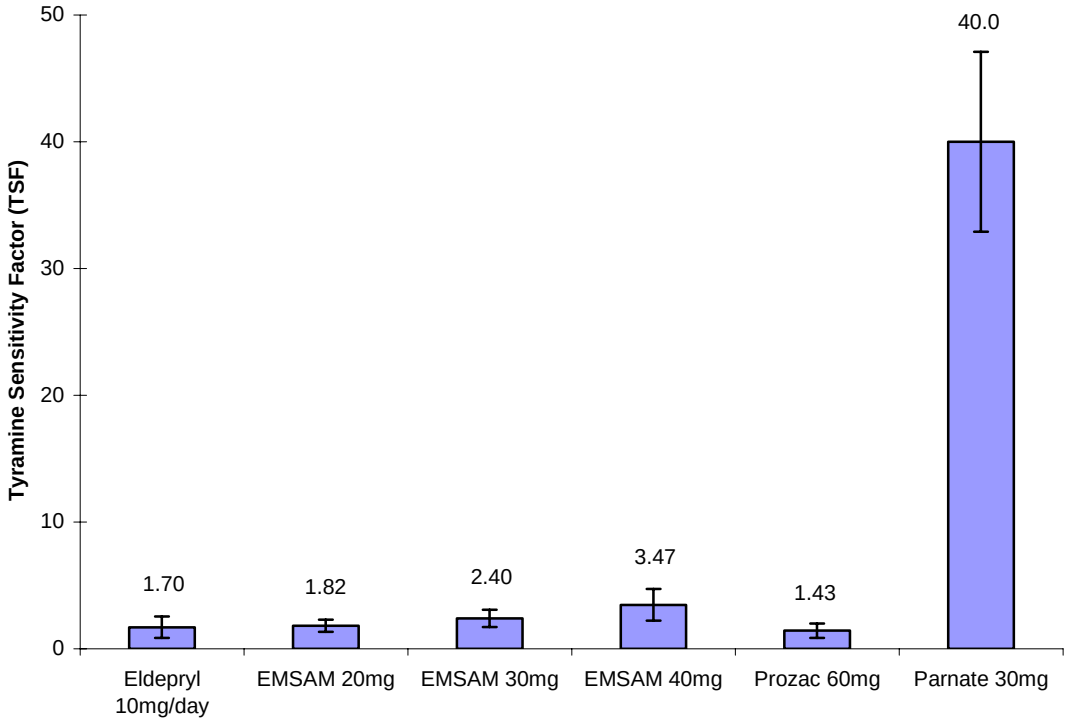
Tyramine challenges following steady-state treatment with each of these agents yielded mean TSF values of 1.8 for EMSAM 20 mg, 1.7 for oral selegiline (study S9303-P9934), 1.4 for fluoxetine (study S9303-P9942), and ≥ 40 for tranylcypromine (study S9303-P9941) (Figure 3). Thus, EMSAM 20 mg produced an increase in cardiovascular

sensitivity to oral tyramine equivalent to that observed following treatment with oral selegiline HCl (5 mg b.i.d.) or fluoxetine HCl (60 mg/day), 2 agents that have been safely administered without dietary modification for many years.

By contrast, tranylcypromine increased the sensitivity to oral tyramine by approximately 20 times that of EMSAM 20 mg. These data further support the administration of EMSAM 20 mg without the need for dietary tyramine modifications, since the relative differences in altered cardiovascular sensitivity to tyramine observed between EMSAM and tranylcypromine clearly differentiated EMSAM from traditional, non-selective MAOI antidepressants.

A comparison of the 8 to 10 day TSF mean values for all studied agents is displayed in Figure 3 below.

Figure 3. Relative Comparison of TSF Values After ~10 Days Treatment



4.3.4 Fasted Versus Fed Data

Study S9303-P9802 examined the tyramine pressor effects of tyramine eaten in a high tyramine content food. Somerset studied tyramine sensitivity in the fed state using 2 different study designs. Days 94 though 96 in study S9303-P0201 examined the tyramine pressor response using encapsulated tyramine given midway through a standard meal.

Data have demonstrated that fasted subjects who ingest tyramine with a meal require 2 to 3 times the amount of tyramine to evoke a hypertensive response compared to administration of tyramine without food (Berlin et al., 1989; Korn et al., 1988a, 1988b).

4.3.4.1 Study S9303-P0201

In a "real life" study design, subjects were provided a meal containing large quantities of cheddar and blue cheese before and during steady-state treatment with EMSAM 20 mg. These cheeses were chosen based on literature data demonstrating that they contain the highest amount of tyramine on a mg/g basis. In an unmedicated baseline challenge, 15 test subjects, recruited on the basis of their self-reported ability to consume large amounts of food, received a breakfast meal consisting of 100 g of aged cheddar cheese and 43 g of English Stilton (454 g = 1 pound). Two subjects were unable to complete this meal over a 1-hour period, and were dropped from the study. The remaining 13 test subjects received a dinner meal of 400 g of aged cheddar cheese and 200 g of blue cheese, and were asked to eat the entire meal. No test subject was able to consume this quantity of cheese over a 2-hour period. However, the amount they were able to consume (average = 499 g) was recorded as their baseline values.

These 13 subjects were then dosed with EMSAM for 12 days, and returned to the clinic to repeat the cheese challenges on study day 13. All 13 test subjects were able to consume the breakfast meal of 100 g of aged cheddar cheese and 43 g of English Stilton, but once again, no subject was able to consume the entire dinner portion of 400 g of cheddar cheese and 200 g of blue cheese over the allotted 2-hour period. However, through encouragement, all subjects were able to consume the baseline amount, thereby allowing a comparison of untreated versus treated impact on blood pressure. At no point in either phase of the study, untreated or treated with EMSAM, did any subject have an increase in blood pressure of 30 mm Hg above baseline.

The results of this study were the basis of Somerset's agreement with the FDA to remove the requirement of dietary modifications from the EMSAM clinical program.

4.3.4.2 Study S9303-P0201

A secondary objective of this study was to obtain the tyramine pressor dose of EMSAM 40 mg-treated subjects after administration of encapsulated tyramine in a fed state. Since the volunteers participating in the fed portion of the study also completed the 90-day tyramine challenge period in the fasted state, a comparison of the tyramine pressor doses and TSF values obtained between the fasted and fed states was also conducted. Eight subjects started and completed the fed portion of this study, and a comparison of the fed versus fasting data for these subjects is summarized in Table 9.

Table 9. Tyramine Pressor Dose Summary Results for EMSAM 40 mg (Fasted versus Fed States)

	N (Subjects)	Tyramine Pressor Dose Mean ± SD (mg tyramine)	Minimum (mg tyramine)	Maximum (mg tyramine)
Period 5 – Fasting Data (90 day assessment)	8	64 ± 27	37.5	100.0
Period 6 – Fed Data (94 day assessment)	8	172 ± 92 [a]	75.0	300.0

[a] Statistically significant from Period 5 ($p < 0.0023$) (N=8).
Paired t-test for statistical comparison.
N = number of subjects and SD = standard deviation.
Data Source: Clinical Trial Report; Appendix C, Tables C.1.12 and C.1.16, Appendix G, Listing G.17.

The mean tyramine pressor dose in fasting EMSAM 40 mg-treated subjects was 64 ± 27 mg. When these same subjects were administered encapsulated tyramine with a standard meal, consumed over a 20-minute period, the mean tyramine pressor dose increased to 172 ± 92 mg of encapsulated tyramine. This was associated with a significant ($p < 0.003$) increase in mean pressor dose of 2.7 times fasted versus fed, and represented > 4 times the amount of tyramine that might be present in a tyramine-rich meal (i.e., up to 40 mg).

It was likely that pressor doses that were obtained with food during the experimental paradigm were conservative, and underestimated the true increase in the margin of

cardiovascular safety of EMSAM when tyramine was consumed as a constituent of food. In the study design described above, tyramine was delivered in capsular form during a meal. This bolus delivery of tyramine to the digestive cavity under these experimental conditions was unlikely to represent the typical extraction and absorption of tyramine over the normal time span of a daily meal.

These results support the hypothesis that EMSAM-treated patients will require greater quantities of dietary tyramine (i.e., mg of tyramine consumed in food) to elicit a hypertensive episode than the mg quantity of encapsulated tyramine administered to normal fasted volunteers. These pharmacodynamic data were consistent with the tyramine bioavailability results obtained in fasted versus fed subjects (study S9303-P0157; VanDenBerg et al., 2003). Therefore, based upon these pharmacodynamic and PK data, a 2- to 3-fold increase in the margin of safety of EMSAM regarding dietary tyramine can be expected in clinical practice. This difference is consistent with previous tyramine challenge studies with other MAOIs that have demonstrated that fasted subjects who ingest tyramine with a meal require 2 to 3 times the amount of tyramine to evoke a hypertensive response compared to administration of tyramine without food (Berlin et al., 1989; Korn et al., 1988a, 1988b).

4.4 Pressor Dose as Measure of Food Consumption

In a practical sense, the mean tyramine pressor dose is useful in estimating the volume of consumed food(s) required to initiate a hypertensive event in an average subject. The food volume is based upon the mg/g content of tyramine found within the food. Using the pressor dose data obtained from the crossover study of EMSAM and tranylcypromine (S9303-P0041), the difference between these 2 agents can be further demonstrated by the amount of food that might be required to produce an acute hypertensive event.

Published data by Shulman et al. reported that old cheddar cheese might contain up to 0.5 mg of tyramine per g of cheese (Shulman et al., 1989). Using this high tyramine content food as an example, some assumptions can be made and applied to the results of study S9303-P0041. Since 10 mg of tyramine in the fasting state produced a hypertensive reaction in all the tranylcypromine-treated subjects, an assumption can be made that 25 mg of tyramine given to these same subjects, under the same circumstances, in the fed state would also produce hypertensive reactions. To ingest 25 mg of tyramine in old

cheddar cheese would require the consumption of approximately 50 g (~1/10th of a lb) of cheese over a period of approximately 30 minutes. Applying the same assumptions to the same test subjects treated with EMSAM in this study, it would require the consumption of 800 g (almost 2 lbs) of the same old cheddar cheese within 30 minutes to produce a hypertensive reaction. In Somerset's study S9303-P9802, subjects could not consume 2 lbs of cheese in 30 minutes. The average quantity of cheese consumed by the 13 test subjects in this study was 1.09 lbs over a period of 2 hours. The largest quantity consumed was 1.27 lbs by 1 subject.

4.5 Safety of Eldepryl and Pharmacodynamic and Pharmacokinetic Comparison to EMSAM

Eldepryl, which contains the same active ingredient (selegiline) as in EMSAM, was approved in the US in 1989. Eldepryl, at a dose of 10 mg/day as adjunctive therapy for the treatment of patients with late-stage Parkinson's disease, is administered without dietary tyramine modifications. At this recommended daily dose, selegiline is safely administered without dietary modifications because the integrity of the intestinal and hepatic MAO-A barrier to ingested amines is maintained. This labeling is supported by the clinical history of the approximately 1.5 million patients with Parkinson's disease who have been exposed to Eldepryl over the past 16 year period that Eldepryl has been available in the US. Review of the Somerset Eldepryl safety database and the Adverse Event Reporting System safety database (FDA database) support the tyramine-related cardiovascular safety of Eldepryl and its labeling permitting normal dietary intake.

As described previously in Section 4.3.3, and supported by studies S9303-P9934 and S9303-P0040, 20 mg of EMSAM is pharmacodynamically equivalent to Eldepryl 10 mg/day. Furthermore the PK variation (coefficient of variances of both Cmax and AUC) of EMSAM 20 mg is less than that of Eldepryl 10 mg/day (Somerset study 9809).

4.6 Summary and Conclusions of Tyramine Challenge Program

In summary, Somerset has provided tyramine safety data following both short- and long-term administration of EMSAM in healthy volunteers. These data demonstrate that:

- At about 10 days, EMSAM 20 mg produced a modest 2-fold increase in sensitivity to orally administered tyramine equivalent to oral selegiline and 20 times less than that of tranylcypromine.
- EMSAM 40 mg produced a change in tyramine sensitivity that was 4 times less than that observed with tranylcypromine, again differentiating EMSAM from traditional, nonselective MAOIs, even at the highest recommended therapeutic dose.
- Maximum increase in tyramine sensitivity due to EMSAM occurred by about 30 days.
- There was a 2- to 3-fold elevation in the margin of cardiovascular safety of EMSAM when tyramine was administered in food or with food, as opposed to encapsulated tyramine in the fasted state.
- The volume of food required to increase blood pressure during treatment with EMSAM 20 mg exceeded physical capabilities.

4.7 Hypertensive Crisis Evaluation in Phase 3

Phase 3 outpatient exposure provides safety support for the use of this product without dietary modifications. More than 2,656 patients were exposed to EMSAM 20 mg. Of those patients, 947 were exposed to EMSAM 30 or 40 mg in Phase 3 clinical trials (controlled and open-label) without dietary modification, and without a single episode of hypertensive crisis.

A retrospective analysis of the safety databases for all of the Phase 3 trials was conducted to obtain any evidence of an occurrence of hypertensive crisis. The computer term search of the database included the following COSTART preferred terms: amblyopia, arrhythmia, bradycardia, chest pain, coma, headache (severe), hypertension, migraine, neck rigidity, palpitation, stupor, and tachycardia.

The search resulted in a listing that displayed the AE(s) of interest with dates and all blood pressures recorded during the study for each patient; treatment assignment was not displayed. After careful blinded review of this AE / blood pressure listing by 2 physician monitors (level-1 review), 110 patients were determined not to meet criteria for further review. Using the following algorithm, 178 patients were selected for comprehensive (level-2) review of case documents.

One patient (10077) had 2 reviewable events (defined below); 1 in double-blind and 1 in open-label studies.

Patients undergoing level-2 comprehensive review met one or more of the following criteria:

1. All patients with the AE terms hypertension, migraine, or severe headache.

2. Patients with one of the other AE terms of clinical interest (amblyopia, arrhythmia, bradycardia, chest pain, coma, neck rigidity, palpitations, stupor, tachycardia), if the AE was of at least moderate severity.

3. Patients with AE terms of clinical interest of any intensity, if treatment of AE was required or there was an occurrence of blood pressure > 160/100 mm Hg during study treatment.

Individual patients may have had > 1 AE of clinical interest. The 178 patients selected by the algorithm had a total of 189 AEs of clinical interest.

The 178 patients in the level-2 review had the following events: 61 had severe headache or migraine (EMSAM 44/2036 [2.2%], placebo 17/831 [2.0%]), 30 had chest pain (EMSAM 21/2036 [1.0%], placebo 9/831 [1.1%]), 19 had palpitations (EMSAM 15/2036 [0.7%], placebo 4/831 [0.5%]), 8 had amblyopia (EMSAM 6/2036 [0.3%], placebo 2/831 [0.2%]), 5 had bradycardia or tachycardia (EMSAM 5/2036 [0.2%]), and 2 had neck rigidity (EMSAM 1/2036 [0.1%], placebo 1/831 [0.1%]). There were no patients with the AE terms arrhythmia, coma, or stupor. None of these patients had acute blood pressure elevations in relationship to the AE of clinical interest that were judged to represent an acute hypertensive episode.

Of the 178 patients in the level-2 review, 63 had a total of 64 reports of the AE "hypertension" (EMSAM 55/2036 [2.7%], placebo 9/831 [1.1%]). One patient (10077) had 2 separate events (hypertension AE), once while receiving placebo and once while receiving EMSAM. A number of patients with the AE "hypertension" had elevated blood pressures prior to enrollment in the study, often untreated. Many patients had single, occasional episodic or mild elevations in blood pressure recorded during study treatment. Of those receiving treatment for hypertension prior to the study, most required no

changes in their antihypertensive medication during the study. A few patients had essential hypertension diagnosed during the study, and appropriate antihypertensive therapy was started. Most of the 64 reported AEs of hypertension occurred in patients with known hypertension, and were judged not to be causally related to EMSAM treatment.

None of these events in the AE term search were judged to be associated with a syndrome representative of hypertensive crisis. However, 5 patients with the AE term "hypertension" (Patient Nos. 14008, 13026, 10048, 10079, and 02006) warrant further comment, either because of an associated serious adverse event or because they discontinued for reason of the AE (Appendix 4).

In summary, no relationship was found between any event in this computer search for possible hypertensive episode and an acute syndrome indicative of hypertensive crisis. Other than 1 case due to beta-agonist drug-drug interaction, this comprehensive review revealed no hypertensive episodes that were judged to be causally related to EMSAM.

5 LABELING/PACKAGING

Physician awareness and patient education are at the core of safe and effective use of pharmaceutical therapies. This is particularly critical in the case of therapies with challenging dosing paradigms or important drug interactions. Somerset recognizes that EMSAM poses unique challenges in this regard due to the need to convey effectively the requirement for dietary modifications at doses of 30 and 40 mg/day. In an effort to maximize this awareness, Somerset will reinforce this message throughout the physician and patient labeling. Additionally, an enhanced format and content for packaging is proposed that will limit the confusion of dosing instructions.

Throughout the proposed EMSAM physician insert, there are multiple citations where the tyramine issue and the need for dietary modifications at doses of 30 or 40 mg/day are clearly conveyed. Statements regarding dietary modifications are located in the CLINICAL PHARMACOLOGY, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS - Information for Patients, and DOSAGE AND ADMINISTRATION sections. In addition, specific guidance related to tyramine-rich foods is provided for patients receiving the 30 or 40 mg doses as a subsection of the WARNINGS section of

the labeling. Furthermore, Somerset proposes a Patient Information Leaflet that contains a prominent section on Dietary Modifications that provides a listing of foods to avoid while receiving a 30 or 40 mg dose of EMSAM.

Because of the potential for certain drug interactions with MAOIs to induce a "serotonin syndrome," EMSAM will be labeled to contraindicate prescription with other antidepressant agents and with certain other drugs such as meperidine and supplements such as St. John's Wort.

EMSAM will be provided in unit of use packaging. The 20, 30, and 40 mg patches will be packaged separately, and will not be sold as mixed units, minimizing the potential for a patient to inadvertently receive a 30 or 40 mg patch without full and proper awareness of the need for dietary modifications. In order to ensure that patients who need to titrate from 20 mg to 30 and 40 mg of EMSAM receive clear guidance on the need for dietary modifications, a extensive combination of physician and patient educational materials will be developed and distributed widely, including Patient Information Leaflets. Further, packaging will be designed to ensure that the dietary instructions are reinforced through unit-of-use packaging with every prescription that is dispensed.

While Somerset acknowledges the unique challenges that will confront patients taking EMSAM, the efforts outlined above in the labeling and packaging for the product will maximize physician and patient awareness of the need for dietary modifications at the 30 and 40 mg doses.

6 BENEFIT AND RISK

EMSAM provides a unique and safe way of delivering an effective MAOI antidepressant without the need for a modified diet by maintaining the functional integrity of the intestinal and hepatic MAO-A barrier to ingested amines. The evidence for this was demonstrated in a series of human pharmacological studies and the Phase 3 program (approximately 2,656 patients; 854 person years). In both short- and long-term clinical studies, EMSAM was an effective antidepressant for the treatment of patients with MDD at doses of 20 to 40 mg/day. The vast majority of these patients ate normal diets throughout the studies, and all of them showed no evidence, by self-report or by detailed

retrospective analysis, of the serious, unmistakable, and potentially fatal outcome of a hypertensive crisis (see Section 4.7).

EMSAM 20 mg is equivalent to Eldepryl 10 mg/day in terms of tyramine sensitivity, and does not require the need for dietary modifications. The safety of oral selegiline is supported by 16 years of clinical experience with 10 mg of oral selegiline (Eldepryl) in the treatment of approximately 1.5 million patients with Parkinson's disease. While post-marketing safety reviews have limitations, the clinical safety record of Eldepryl is relevant. The proposed label recommends no dietary tyramine modification at the 20 mg EMSAM dose, but does recommend dietary modifications at the 30 and 40 mg doses, respecting the more limited clinical experience with these higher doses. In order to ensure that patients who need to titrate from 20 mg to 30 and 40 mg of EMSAM receive clear guidance on the need for dietary modifications, a extensive combination of physician and patient educational materials will be developed and distributed widely, including Patient Information Leaflets. Further, packaging will be designed to ensure that the dietary instructions are reinforced through unit-of-use packaging with every prescription that is dispensed.

In summary, EMSAM provides a new and safe therapeutic option for treating patients with MDD. The benefit of providing a new MAOI at an effective dose (EMSAM 20 mg) that can safely be taken without dietary modifications, and which carries a tyramine safety profile that is comparable to that of the same approved chemical without dietary restrictions, outweighs the risk of inaccurate labeling that would discourage patients who would benefit from this medication. The more limited clinical and experimental experience at this time with effective antidepressant doses of EMSAM that are higher (30 mg or 40 mg) suggests that it would be prudent to label these doses for dietary tyramine modifications.

7 CONCLUSION

EMSAM 20 mg can be safely administered without dietary modification.

8 LIST OF ABBREVIATIONS

AE	adverse event
AUC	area under the concentration-time curve
b.i.d.	twice daily
CGI-c	Clinical Global Impressions Scale
CGI-s	Clinical Global Impression of Change
Cmax	maximum plasma concentration
COSTART	Coding Symbols for a Thesaurus of Adverse Reactions Terms
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition
EMSAM®	(selegiline transdermal system)
FDA	Food and Drug Administration
GI	gastrointestinal
HAM-D	Hamilton Depression Rating Scale
5HT	serotonin
MADRS	Montgomery-Asburg Depression Rating Scale
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
MDD	major depressive disorder
NDA	New Drug Application
NE	norepinephrine
PK	pharmacokinetic(s)(ly)
SBP	systolic blood pressure
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TSF	tyramine sensitivity factor

9 REFERENCES

Barrett JS, Hochadel TJ, Morales RJ, Rohatagi S, DeWitt KE, Watson SK, DiSanto AR. Pharmacokinetics and safety of selegiline transdermal system relative to single-dose oral administration in the elderly. Am J Ther 1996;3:688-698.

Berlin I, Zimmer R, Cournot A, Payan C, Pederriosse AM, Puech AJ. Determination and comparison of the pressor effect of tyramine during long term meclobemide and tranylcypromine treatment in healthy volunteers. Clin Pharmacol Ther 1989;46:344-351.

Birkmayer W, Riederer P, Linauer W, Knoll J. L-deprenyl plus l-phenylalanine in the treatment of depression. J Neurol Transm 1984;59:81-87.

Blackwell B, Marley E, Price J, Taylor D. Hypertensive interactions between monoamine oxidase inhibitors and foodstuffs. Br J Psychiatry 1967;113:349-365.

Cassano P, Fava M. Tolerability issues during long-term treatment with antidepressants. Ann Clin Psychiatry 2004;16:15-25.

Chrisp P, Mammen GJ, Sorkin EM. Selegiline – A review of its pharmacology, symptomatic benefits and protective potential in Parkinson's disease. Drugs Aging 1991;1:228-248.

Cuijpers P, Schoevers RA. Increased mortality in depressive disorders: A review. Curr Psychiatry Rep 2004;6:430-437.

Dollery CT, Brown MJ, Davis DS, Lewis PJ, Strollin-Benedetti M. Oral absorption and concentration-effect relationship of tyramine with and without cimoxatone, a type-A specific inhibitor of monoamine oxidase. Clin Pharmacol Ther 1983;34:651-662.

Folks DG. Monoamine oxidase inhibitors: Reappraisal of dietary considerations. J Clin Psychopharmacol 1983;3:249-352.

Gardner DM, Shulman KI, Walker SE, Tailor SA. The making of a user friendly MAOI diet. J Clin Psychiatry 1996;57:99-104.

Greenberg PE, Kessler RC, Birnbaum HG, Leong SA, Lowe SW, Berglund PA, Corey-Lisle PK. The economic burden of depression in the United States: How did it change between 1990 and 2000? J Clin Psychiatry 2003;64:1465-1475.

Guze SB, Robins E. Suicide and primary affective disorders. Br J Psychiatry 1970;117:437-438.

Hoffman BB, Lefkowitz RJ. Catecholamines and sympathomimetic drugs. In: Gilman AG, Rall JW, Nies AS, Taylor P, eds. The Pharmacological Basis of Therapeutics (8th Edition). Pergamon Press 1990;187-220.

Huebert ND, Dulery BD, Schoun J, Schwack V, Hinze C, Haegele KD. Kinetics and metabolism of p-tyramine during monoamine oxidase inhibition by mofegiline. Clin Pharmacol Ther 1994;56:537-542.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8-19.

Kessler RC, Berglund P, Demler O, Jin R, et al. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095-3105.

Knoll J. Deprenyl (selegiline): The history of its development and pharmacological action Acta Neurol Scand Suppl 1983;95:57-80.

Korn A, DaPrada M, Raffesberg W, Allen S, Gasic S. Tyramine pressor effect in man: Studies with moclobemide a novel, irreversible monoamine oxidase inhibitor. J Neural Transm 1988a;26(Suppl):57-71.

Korn A, DaPrada M, Raffesberg M, Gasic S, Eichler HG. The effect of moclobemide a new reversible monoamine oxidase inhibitor on absorption and pressor effects of tyramine. Cardiovasc Pharmacol 1988b;11:17-23.

Mahmood I. Clinical pharmacokinetics and pharmacodynamics of selegiline. Clin Pharmacokinet 1997;33:91–102.

Mann JJ, Aarons SF, Wilner PJ, Keilp JG, et al. A controlled study of the antidepressant efficacy and side effects of (-)-deprenyl. Arch Gen Psychiatry 1989;46:45-50.

Mann JJ, Gershon S. Antidepressant properties of a selective monoamine oxidase inhibitor: l-Deprenyl. IRCS Med Sci 1987;7:450.

Mann JJ, Frances A, Kaplan RD, Kocsis J, Peselow ED, Gershon S. The relative efficacy of l-deprenyl, a selective monoamine oxidase type B inhibitor, in endogenous and nonendogenous depression. J Clin Psychopharmacol 1982;2:54-57.

Mawhinney M, Cole D, Azzaro AJ. Daily transdermal administration of selegiline to guinea-pigs preferentially inhibits monoamine oxidase activity in brain when compared with intestinal and hepatic tissues. J Pharm Pharmacol 2003;55:27-34.

McCabe BJ. Dietary tyramine and other pressor amines in MAOI regimens: A review. J Amer Dietetic Assoc 1986;86:1059-1064.

McGrath PJ, Stewart JW, Harrison W, Wager S, Nunes EN, Quitkin FM. A placebo-controlled trial of L-deprenyl in atypical depression. Psychopharm Bull 1989;11:63-67.

McIntyre R, O'Donovan C. The human cost of not achieving full remission in depression. Canadian Journal of Psychiatry 2004;49(Suppl 1):10S-16S.

Mendis N, Pare CM, Sandler M, Glover V, Stern GM. Is the failure of (-)-deprenyl, a selective monoamine oxidase B inhibitor, to alleviate depression related to freedom from cheese effect? Psychopharmacology 1981;73:87-90.

Mendlewicz PJ, Youdim MBH. L-deprenyl, a selective monoamine oxidase type B inhibitor in the treatment of depression: a double-blind evaluation. Brit J Psychiatry 1983;142:508-511.

Mendlewicz J, Youdim MBH. Anti-depressant potentiation of 5-hydroxytryptophan by l-deprenyl, an MAO “type b” inhibitor. J Neural Trans 1978;43:279-286.

Montgomery S, Doyle JJ, Stern L, McBurney CR. Economic considerations in the prescribing of third-generation antidepressants. Pharmacoeconomics 2005;23:477-491.

Mukherjee J, Yang ZY. Monoamine oxidase A inhibition by fluoxetine: An in vitro and in vivo study. Synapse 1999;31:285-289.

Murphy DL, Aulakh CS, Garrick NA, Sunderland T. Monoamine oxidase inhibitors as antidepressants. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress, 1st ed, 1987;545-552.

Murray C, Lopez A, Alternative projections of mortality and disability by cause 1990-2000. Global Burden of Disease Study 1997;349:1498-1504.

Prasad A, Glover V, Goodwin BL, Sandler M, Signy M, Smith SE. Enhanced pressor sensitivity to oral tyramine challenge following high dose selegiline treatment. Psychopharmacology 1988;95:540-543.

Quitkin FM, Liebowitz MR, Stewart JW, McGrath PJ, et al. L-deprenyl in atypical depressives. Arch Gen Psychiatry 1984;41:777-781.

Robinson DS. Monoamine oxidase inhibitors: A new generation. Psychopharmacol Bull 2002;36:124-138.

Sabelli HC. Rapid treatment of depression with selegiline-phenylalanine combination. J Clin Psychiatry 1991;52:137.

Schildkraut JJ. The catecholamine hypothesis of affective disorders: A review of supporting evidence. American Journal of Psychiatry 1965;122:509-522.

Schulz R, Antonin KH, Hoffmann E, Jedrychowski M, Nilsson E, Schick C, Bieck PR. Tyramine kinetics and pressor sensitivity during monoamine oxidase inhibition by selegiline. Clin Pharmacol Ther 1989;46:528-536.

Shin HS. Metabolism of selegiline in humans — Identification, excretion and stereochemistry of urinary metabolites. Drug Metab Disp 1997;25:657-662.

Shulman KI, Walker SE. Refining the MAOI diet: Tyramine content of pizzas and soy products. J Clin Psychiatry 1999;60:191-193.

Shulman KI, Walker SE, MacKenzie S, Knowles S. Dietary restrictions, tyramine, and the use of monoamine oxidase inhibitors. J Clin Psychopharmacol 1989;9:397-402.

Simon GE, Goldberg DP, Von Korff M, Ustun TB. Understanding cross-national differences in depression prevalence. Psychological Medicine 2002;32:585-594.

Standaert DG, Young AB. Treatment of central nervous system degenerative disorders. In: Hardman JG, Limbird LE, eds. Goodman and Gilman's 'The Pharmacological Basis of Therapeutics' 10th ed. 2001;549-568.

Sunderland T, Mueller EA, Cohen RM, Jimerson DC, Pickar D, Murphy DL. Tyramine pressor sensitivity changes during deprenyl treatment. Psychopharmacology 1985;86:432-437.

Sunderland T, Cohen RM, Molchan S, Lawlor BA, et al. A high-dose selegiline in treatment-resistant older depressive subjects. Arch Gen Psychiatry 1994;51:607-615.

Thase M., Trevedi M, Rush A. MAOIs in the contemporary treatment of depression. Neuropsychopharmacology 1995;12:185-219.

Thase M. Therapeutic alternatives for difficult-to-treat depression: A narrative review of the state of the evidence. CNS Spectrums 2004;9:808-821.

VanDenBerg CM, Blob LF, Kemper EM, Azzaro AJ. Tyramine pharmacokinetics and reduced bioavailability with food. J Clin Pharmacol 2003;43:604-609.

World Health Organization. The World Health Report. Mental Health: New Understanding, New Hope. 2001.

Zeller EA. Ulber Den Enzmatischen Abbau Von Histamin Und Diasninen. Z Mitteilung Helvetica Chemica Acta 1938;21:880-890.

SOMERSET STUDIES:

PHARM-19. Assay of MAO-A and MAO-B in rat brain and intestine following chronic selegiline patch application.

S9303-010-94B. Tyramine challenge during single dose application of one-quarter, one-half and one selegiline transdermal system (10 cm^2 system: 1.83 mg/cm^2) to healthy male volunteers.

S9303-028-95B. Dose proportionality of three different selegiline transdermal system formulations (0.5, 1.0 and 1.5mg/cm^2 selegiline) in healthy elderly men and women.

S9303-030-95B. Pharmacokinetic evaluation and wearability of three different selegiline transdermal system (STS) formulations (0.5, 1.0 and 1.5mg/cm^2 selegiline) in healthy males.

S9303-031-95B. Pharmacokinetic evaluation of multiple dose (ten-day) administration of three different selegiline transdermal system (STS) formulations in healthy elderly men.

S9303-033-96B. Tyramine pressor response following multiple dose administration of a 1.0 mg/cm^2 (15 cm^2) and a 1.5 mg/cm^2 (20 cm^2) selegiline transdermal system (STS) to healthy elderly volunteers.

S9303-E106-96B. A double-blind, placebo-controlled, parallel assessment of the safety and efficacy of the selegiline transdermal system in patients with major depression.

S9303-037-97B. Tyramine pressor response following multiple dose administration of a 1.0 mg/cm^2 (20 cm^2) selegiline transdermal system (STS) to healthy male volunteers.

S9303-P9802. Tyramine enriched meal blood pressure response following multiple dose administration of a 1.0mg/cm^2 (20cm^2) selegiline transdermal system (STS) to healthy male volunteers.

S9303-P9806. A double-blind, placebo-controlled, parallel-group assessment of the selegiline transdermal system in the reappearance of symptoms associated with major depression.

S9303-P9807. Steady-state pharmacokinetic comparison of the 10 mg and 20 mg selegiline transdermal system in healthy volunteers.

S9303-P9809. Single dose pharmacokinetic comparison of transdermal selegiline 20 mg patches versus intravenous infusion (10 mg/24 hours) versus oral (10 mg) administration to healthy male volunteers.

S9303-P9810. Single dose pharmacokinetic/metabolism study of ^{14}C-selegiline in healthy male volunteers.

S9303-P9811. Pharmacokinetics of STS in renally impaired subjects.

S9303-P9812. Single dose pharmacokinetic study of transdermal selegiline 20 mg patches in hepatic disease patients.

S9303-P9814. Pharmacokinetics of STS in pediatric subjects.

S9303-P9816. Oral tyramine pressor response during administration of increasing doses of encapsulated tyramine powder administered with meals to healthy male volunteers.

S9303-P9919. Effect of chronic transdermal selegiline 20 mg administration on the pharmacokinetic of racemic warfarin after steady-state administration in healthy volunteers.

S9303-P9920. Steady-state pharmacokinetic drug interaction study between alprazolam and selegiline transdermal system in healthy volunteers.

S9303-P9922. Steady-state pharmacokinetic drug interaction study between olanzapine and selegiline transdermal system in healthy volunteers.

S9303-P9923. Steady-state pharmacokinetic comparison of the 10 mg and 20 mg selegiline transdermal system in healthy male volunteers.

S9303-P9925. Steady-state pharmacokinetic drug interaction study between levothyroxine and selegiline transdermal system in healthy volunteers.

S9303-P9926. Pharmacokinetic drug interaction study between ibuprofen and selegiline transdermal system in healthy volunteers.

S9303-P9927. Pharmacokinetic/pharmacodynamic drug interaction study between alcohol and selegiline transdermal system in healthy volunteers.

S9303-P9928. Steady-state pharmacokinetic and pharmacodynamic drug interaction study between pseudoephedrine and selegiline transdermal system in healthy volunteers.

S9303-P9931. Steady-state pharmacokinetic drug interaction study between ketoconazole and selegiline transdermal system in healthy volunteers.

S9303-P9932. Oral tyramine pressor response during administration of tyramine to healthy male volunteers before and after chronic administration of selegiline transdermal system.

S9303-P9933. Single dose pharmacokinetic drug interaction study between carbamazepine and selegiline transdermal system in healthy volunteers.

S9303-P9934. Oral tyramine pressor response during administration of tyramine to healthy volunteers before and after chronic administration of Eldepryl® capsules 5 mg BID.

S9303-P9940. Oral tyramine pressor response during administration of tyramine to healthy male volunteers before and after chronic administration of selegiline transdermal system.

S9303-P9941. Oral tyramine pressor response during administration of tyramine to healthy male volunteers before and after chronic administration of Prozac capsules 20 mg daily.

S9303-P9942. Oral tyramine pressor response during administration of tyramine to healthy volunteers before and after chronic administration of fluoxetine capsules 60 mg daily.

S9303-P0045. Oral tyramine pressor response during administration of tyramine to healthy male volunteers before and after 30-day administration of selegiline transdermal system.

S9303-P0046. Steady-state pharmacokinetic and pharmacodynamic drug interaction study between phenylpropanolamine and selegiline transdermal system in healthy volunteers.

S9303-P0048. Oral tyramine pressor response during administration of tyramine to healthy volunteers before and after steady-state administration of 30 mg selegiline transdermal system.

S9303-P0050. Pressor response after administration of oral tyramine to healthy volunteers before and during steady-state administration of 40 mg selegiline transdermal system.

S9303-P0051. Steady-state pharmacokinetic comparison of alternate application sites for the selegiline transdermal system in healthy volunteers.

S9303-P0052. Phase III flexible dose titration study of the safety and efficacy of the selegiline transdermal system in patients with major depression.

S9303-P0201. Oral tyramine pressor response of healthy volunteers before and during 30, 60, and 90 day administration of the selegiline transdermal system 40 mg.

S9303-P0204. Phase III, open-label study of the safety, tolerability, and efficacy of the selegiline transdermal system 20 mg, 30 mg, or 40 mg in subjects with major depression.

APPENDIX 1

Comparative Pharmacokinetic (PK) Parameters - Study S9303-P9809

PK Parameter	Route	Selegiline	N-Desmethylselegiline	R-Amphetamine	R-Methamphetamine
AUCinf (pg/hr/mL)	Trans	46162	22960	42692	93088
	IV	106024	54577	85822	204048
	Oral	4537	67685	115843	289197
Cmax (pg/mL)	Trans	2162	791.4	796	2171
	IV	4570	1833	1900	4972
	Oral	2222	22992	3741	13150
Tmax (hr)	Trans	18.38	19.58	29.17	27.5
	IV	19.90	21.32	28.17	26.83
	Oral	0.86	0.88	5.85	2.54
T½ (hr)	Trans	20.1	15.07	25.33	20.47
	IV	24.64	18.82	23.52	20.69
	Oral	8.65	8.73	15.48	14.24
%Fe	Trans	0.0665	0.351	7.184	17.569
	IV	0.5501	0.616	11.078	26.199
	Oral	0.0191	0.740	14.408	32.886

Comparative Pharmacokinetic (PK) Parameters - Study S9303-P9809

PK Parameter	Route	Selegiline	N-Desmethylselegiline	R-Amphetamine	R-Methamphetamine
AUCinf M/P	Trans	-	0.55	0.96	2.39
	IV	-	0.51	0.83	2
	Oral	-	86.07	320.56	903.05

Doses: Trans - transdermal selegiline system 20 mg/20 cm^2; intravenous (IV) - 10 mg selegiline/24 hours; and oral - 10 mg selegiline.
AUCinf = area under the concentration-time curve from time zero extrapolated to infinity, AUCinf M/P = ratio of metabolite to parent compound area under the concentration-time curve from time zero extrapolated to infinity, Cmax = maximum plasma concentration, %Fe = fraction excreted in the urine unchanged, T½ = half life, and Tmax = time of maximum observed concentration.

APPENDIX 2A

Body Weight

In placebo-controlled studies (6-8 weeks), the incidence of patients who experienced ≥ 5% weight gain or weight loss with EMSAM treatment is shown in the table below.

Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials with EMSAM

Weight Change	EMSAM	Placebo
	(N=757)	(N=614)
Gained ≥ 5%	2.1%	2.4%
Lost ≥ 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. In longer-term studies, the body weight of 675 patients was recorded before and after treatment with EMSAM for 3-12 months, and the average weight change was –1.6 lbs.

APPENDIX 2B

Sexual Dysfunction

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, in particular, many of the currently available anti-depressants. 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 are likely to underestimate their actual incidence. The table below shows that the incidence rates of sexual side effects in patients with MDD are comparable to the placebo rates in placebo-controlled trials. Currently, there are no controlled studies designed to examine sexual dysfunction with EMSAM treatment.

Incidence of Sexual Side Effects in Placebo-controlled Clinical Trials

Adverse Event [a]	**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%
Sexual Function Abnormal	0.3%	0.4%
	IN FEMALES ONLY	
	(N=513)	**(N=412)**
Decreased Libido	0.0%	0.2%
Anorgasmia	0.2%	0.0%
Sexual Function Abnormal	0.0%	0.2%

[a] Coding Symbols for a Thesaurus of Adverse Reactions Terms (COSTART) preferred term.

APPENDIX 3

Tyramine Pressor Dose (mg) for 47 Subjects Before and After Administration of EMSAM 20 mg and Resulting TSF Ratio (Fasting)

Subject	Study S9303-	Baseline 1[a]	Baseline 2[a]	Baseline Average	EMSAM 20 mg[b]	Change from Baseline	TSF Average[c]
1	P9932	500	400	450	300	-150	1.50
2	P9932	400	400	400	200	-200	2.00
3	P9932	500	600	550	200	-350	2.75
4	P9932	300	300	300	200	-100	1.50
5	P9932	600	400	500	400	-100	1.25
6	P9932	400	600	500	200	-300	2.50
7	P9932	400	700	550	400	-150	1.38
8	P9932	300	300	300	300	0	1.00
9	P9932	500	400	450	200	-250	2.25
10	P9932	500	500	500	300	-200	1.67
11	P9932	600	500	550	200	-350	2.75
12	P9932	600	700	650	300	-350	2.17
13	P9932	700	700	700	500	-200	1.40
14	P9932	200	500	350	200	-150	1.75
15	P9932	500	400	450	200	-250	2.25

Tyramine Pressor Dose (mg) for 47 Subjects Before and After Administration of EMSAM 20 mg and Resulting TSF Ratio (Fasting)

Subject	Study S9303-	Baseline 1[a]	Baseline 2[a]	Baseline Average	EMSAM 20 mg[b]	Change from Baseline	TSF Average[c]
16	P9932	600	700	650	400	-250	1.63
17	P9932	500	700	600	600	0	1.00
18	P9932	400	600	500	200	-300	2.50
19	P9932	200	500	350	200	-150	1.75
20	P9932	700	700	700	300	-400	2.33
21	P9932	500	500	500	300	-200	1.67
22	P9932	500	500	500	300	-200	1.67
23	P9932	400	500	450	200	-250	2.25
24	P9932	500	400	450	300	-150	1.50
25	P9940	600	500	550	300	-250	1.83
26	P9940	700	700	700	600	-100	1.17
27	P9940	600	700	650	400	-250	1.63
28	P9940	700	500	600	400	-200	1.50
29	P9940	600	600	600	400	-200	1.50
30	P9940	600	700	650	400	-250	1.63

Tyramine Pressor Dose (mg) for 47 Subjects Before and After Administration of EMSAM 20 mg and Resulting TSF Ratio (Fasting)

Subject	Study S9303-	Baseline 1[a]	Baseline 2[a]	Baseline Average	EMSAM 20 mg[b]	Change from Baseline	TSF Average[c]
31	P9940	500	600	550	300	-250	1.83
32	P9940	400	300	350	300	-50	1.17
33	P9940	400	500	450	400	-50	1.13
34	P9940	400	700	550	300	-250	1.83
35	P9940	400	400	400	200	-200	2.00
36	P9940	600	600	600	200	-400	3.00
37	P9940	400	600	500	200	-300	2.50
38	P9941	600	600	600	400	-200	1.50
39	P9941	600	600	600	300	-300	2.00
40	P9941	500	300	400	200	-200	2.00
41	P9941	400	400	400	200	-200	2.00
42	P9941	300	400	350	200	-150	1.75
43	P9941	700	400	550	400	-150	1.38
44	P9941	400	400	400	300	-100	1.33
45	P9941	600	400	500	300	-200	1.67

Tyramine Pressor Dose (mg) for 47 Subjects Before and After Administration of EMSAM 20 mg and Resulting TSF Ratio (Fasting)

Subject	Study S9303-	Baseline 1[a]	Baseline 2[a]	Baseline Average	EMSAM 20 mg[b]	Change from Baseline	TSF Average[c]
46	P9941	500	500	500	200	-300	2.50
47	P9941	300	700	500	200	-300	2.50
	Mean	**491**	**523**	**507**	**298**	**-210**	**1.82**
	SD	**130**	**131**	**106**	**105**	**94**	**0.49**

[a] Tyramine pressor dose prior to administration of EMSAM (20 mg/20cm^2).

[b] Tyramine pressor dose after steady-state administration of EMSAM (20 mg/20 cm^2).

[c] TSF = tyramine sensitivity factor calculated as the ratio of the baseline average pressor dose to EMSAM 20 mg interaction pressor dose.

Note: Subjects were exposed to EMSAM (20 mg/20 cm^2) for a period of 9 to 10 days. All tyramine values are expressed as the free base equivalent.
SD = standard deviation.

APPENDIX 4

Patient Narratives Resulting from Evaluation of Phase 3 Database

- **Patient 14008**

AE: Hypertension

This 51-year-old female patient discontinued the study drug, EMSAM 20 mg, during the first week of double-blind continuation treatment with EMSAM following 10 weeks of open-label EMSAM treatment. She was hospitalized to rule out myocardial infarction following 2 incidents of chest pain and shortness of breath over the preceding 24 hours, which did not respond to nitroglycerin. Blood pressure in the emergency room (ER) was reported by the patient to be 160/114 mm Hg. She was discharged in stable condition after 2 days on amlodipine (Norvasc®) to control hypertension.

The patient had a > 10-year history of hypertension, and had been treated with atenolol since 1994, which was continued throughout the study. Baseline BP was 166/101 mm Hg, and the patient had mildly elevated blood pressures throughout the study (highest 151/95 mm Hg).

The assessment of the physician monitors upon review of the data in study records was essential hypertension, poorly controlled.

- **Patient 13026**

AE: Hypertension

This 71-year-old female patient discontinued the study drug, EMSAM 20 mg, during Week 8 of open-label EMSAM treatment because of the adverse event (AE) "worsening hypertension." The patient had a history of hypertension since 1993, treated long-term with atenolol (Tenormin®), which was continued during the study. Screening blood pressure was 147/91 mm Hg. She remained borderline hypertensive throughout the study. At the Week 8 visit, her blood pressure was 170/100 mm Hg, and the investigator elected to terminate the patient from the study (08 May 2000) for apparently asymptomatic

worsening of her hypertension. The previous week, the patient had been cystoscoped for atypical cytology.

The investigator contacted the patient in follow-up on 31 August 2000. At that time, she informed the study site that she had been hospitalized on 11 May 2000, after experiencing faintness and presyncope for 2 days and for control of hypertension. She was discharged after 5 days with her blood pressure apparently stabilized. The patient refused a request for medical records. A serious adverse event (SAE) form was submitted 31 August 2000.

The assessment of the physician monitors upon review of the data in the study records and source documents was that the patient had poorly controlled essential hypertension unrelated to EMSAM treatment.

- **Patient 10048**

AE: Hypertension

This 33-year-old Caucasian female patient discontinued the study drug, EMSAM 40 mg, on Day 39 due to the AE "elevated blood pressure." Relevant medical history included chronic low blood pressure and associated complaints of fatigue and intermittent dizziness on standing. No abnormal blood pressures were recorded during screening or throughout study treatment. She received no concomitant medications with cardiovascular effects. On investigation of the "elevated blood pressure" complaint, the investigator noted that the patient was at home complaining of this AE on 23 March 2002, and did not have a blood pressure recorded, nor was there any medical contact or treatment sought at that time.

The Study Termination Summary stated that the patient's blood pressure was 72/54 mm Hg when seen the following day (24 March 2002) at the study site. In the investigator's opinion, there was no evidence that the patient experienced elevated blood pressure. The recorded AE reflected the patient's report, not objective findings. The investigator attributed this event to the patient's unstable psychiatric status manifested by ongoing high levels of anxiety.

The assessment of the physician monitors upon review of the data in the study records and source documents was that the patient never had a documented elevation of blood pressure.

- **Patient 10079**

AE: Hypertension

This 41-year-old female patient discontinued the study drug, EMSAM 30 mg, on Day 127. Her medical history at screening was unremarkable. She was borderline normotensive at baseline (146/94 mm Hg), and her blood pressures during study treatment remained slightly elevated. At the Week 18 termination visit, her blood pressure was 171/109 mm Hg. At that time, she revealed that 1 week earlier she had sought care with her private physician for shortness of breath, and was prescribed albuterol inhaler, a protocol prohibited drug. While at home, 3 days before her termination visit, she experienced an acute episode of severe headache, sweating, stiff neck, and palpitations. These resolved spontaneously within 15 minutes, and she reported to work where a nurse recorded her blood pressure as 170/100 mm Hg. She stopped the albuterol, and 2 days later, the investigator elected to discontinue her from study treatment because of elevated blood pressure.

The patient's medical records were subsequently obtained. The records revealed that high blood pressure had been noted on several occasions, with blood pressure as high as 146/102 mm Hg. The records did not show that she had received antihypertensive treatment.

The assessment of the physician monitors upon review of the data contained in study records and source documents was that the patient, with history of labile hypertension, experienced acute blood pressure elevations secondary to an albuterol-selegiline interaction. The beta-agonist, albuterol, is contraindicated during treatment with a monoamine oxidase inhibitor (MAOI).

- **Patient 02006**

AE: Hypertension

This 69-year-old female patient began EMSAM 20 mg on 12 September 2002, which was increased to EMSAM 30 mg after 1 week. Her psychiatric history was remarkable for treatment with alprazolam 1 mg daily for at least 4 years; the dose was tapered to 0.5 mg/day for 1 week, and then discontinued on 04 September 2002 prior to study treatment. On 30 September 2002 at 3:00 AM, she experienced shortness of breath, headache, tingling, and numbness over her entire body. She removed the EMSAM, and went to the ER, where a blood pressure of 119/115 mm Hg was recorded. At 4:50 AM, her blood pressure was 178/97 mm Hg. At that time, she related that she had eaten her evening meal approximately 6 hours prior to onset of her symptoms, and it had included a portion of meat (brisket) that had been marinated in soy sauce. At 5:30 AM, her blood pressure was 178/97 mm Hg, and she was given nitroglycerin spray and lorazepam (Ativan®) 1 mg sublingually. Her blood pressure decreased shortly thereafter to 144/77 mm Hg, and she was discharged without further problems. The ER physician noted that there might have been a relationship between MAOI treatment and food.

On 02 October 2002, the patient requested restarting EMSAM; on 05 October 2002, EMSAM 30 mg was restarted. On 06 October 2002, she applied EMSAM at 9:40 AM, at which time her blood pressure was 128/78 mm Hg (self-recorded). At 9:30 PM, she had "numbness all over," and her BP was 180/100 mm Hg. At 10:50 PM, her blood pressure was 190/100 mm Hg, and she contacted the study site, and was instructed to remove the EMSAM. She denied eating anything unusual, and continued to monitor her blood pressure. On 07 October 2002 midday, when her blood pressure was 170/100 mm Hg, she again experienced tingling all over, felt nervous, and requested restarting alprazolam. The investigator felt that the patient was experiencing panic attacks manifest by extreme anxiety, and prescribed alprazolam, and discontinued the patient from the study.

Both the investigator and the physician monitors agreed that the syndrome represented recurrent panic attacks with marked anxiety related to abrupt discontinuation of chronic benzodiazepine therapy. The fact that over a 7-day period this subject had experienced 3

episodes of a symptom complex that included generalized numbness and tingling, shortness of breath, and extreme nervousness pointed to the likelihood that the hypertension was a manifestation of the panic attacks.