

**Review and Evaluation of Clinical Data
NDA #21-336**

Sponsor: Somerset Pharmaceuticals
Drug: Selegiline Transdermal System (EMSAM)
Proposed Indication: Major Depression (Acute Claim)
Material Submitted: Response to 1-30-04 Approvable Letter
Correspondence Date: May 26, 2005
Date Received: May 27, 2005
Related NDA: #21-708 (Maintenance Claim)

I. Background

Selegiline is a monoamine oxidase inhibitor (MAOI) which has been developed as a transdermal patch formulation for the treatment of major depression: Selegiline Transdermal System or STS, with the proposed trade name EMSAM (STS and EMSAM are used interchangeably in this review). The commercial sponsor, Somerset Pharmaceuticals, submitted an original NDA supporting the use of STS for this indication on 5-24-01. The review of this application revealed that only one of four key efficacy studies was positive.¹

Accordingly, this NDA was declared non-approvable (NA) due to insufficient evidence of efficacy and an action letter was issued on 3-25-02. In addition to the efficacy deficiency, this letter also described a number of other clinical, nonclinical pharmacology; and chemistry, manufacturing and controls (CMC) issues to be addressed.

On 7-31-03, Somerset responded to our NA letter. This submission contained a new acute depression study which utilized flexible dosing up to the 40mg patch (previous studies used a maximum patch strength of only 20mg). This submission was reviewed and the new study was deemed positive. In addition, that submission contained a new relapse prevention trial to support a maintenance claim; this study was also deemed to be positive. At that point, the application was declared to be approvable.² However, since the maximum labeled strength would now be 40mg, it seemed necessary to require dietary restrictions for

¹ See my Review and Evaluation of Clinical Efficacy Data dated 2-28-02.

² See my Review and Evaluation of Clinical Efficacy Data dated 12-16-03.

tyramine based on tyramine challenge data at this patch strength. An approvable letter was issued on 1-30-04

The current submission was received on 5-27-05. On 6-6-05, this submission was deemed to be a complete response to our 1-30-04 approvable letter. Clinical issues contained in this submission are addressed below.

II. Review of Clinical Issues

1. Clinical Trials Safety Data

a. Sources of Updated Safety Data

No STS clinical studies for any indication have been initiated since the sponsor's 7-31-03 NA response.

At the time of the NA response, three trials were ongoing:

- P0158 - one year, open-label study of flexible dose STS 20, 30, and 40mg in depression. This study is now complete (N=191). Safety data for the period 1-31-03 to study completion (8-28-03) are presented in the current submission. No new patients entered the trial during that timeframe.

- P0204 - one year, open-label study of flexible dose STS 20, 30, and 40mg in depression. This study is ongoing. Safety data are provided in this submission from 3-31-03 through 12-31-04. An additional 621 new patients were studied during this period.
- P0043 - open-label, open-ended, compassionate use study of STS 20mg in depression. This study is ongoing. Safety data are provided here for the period 3-31-03 to 3-31-05. There are currently seven patients still in this study, the longest of which has been participating for over four years.

Information on serious adverse events was submitted from these three trials during the above time intervals. Also, information on adverse events leading to dropout and common adverse events were provided from studies P0158 and P0204. These data are summarized below.

b. Serious Adverse Events

There were no deaths reported.

A total of 18 patients experienced non-fatal serious adverse events (SAE's). A line listing of these events is presented in Appendix 1 to this review.

The narrative summary for each of these 18 patients was examined by the undersigned reviewer; in some instances, the Case Report Form was also examined when further information was needed. Sixteen of the 18 patients were from study P0204.

Among all 18 patients with new SAE's, the following six patients, all from study P0204, warrant some discussion:

Patient 02064 was a 58 year old Caucasian female who was treated with STS for 371 days at a dose of 30mg during most of that time. At her week 52 assessment (day 372), she was noted to have blood pressure elevation (183/92 supine and 177/102 standing). At baseline, her blood pressure was 152/82 supine and 147/88 standing and readings remained relatively stable until the last assessment. She was hospitalized and treated with a calcium channel blocker on day 372, with resolution of her blood pressure elevation on that day. Her dietary survey from the time period of the blood pressure elevation revealed ingestion of the following items which, in the presence of MAO inhibition,

may produce or contribute to a rise in blood pressure: cheddar cheese (ingested 3 times), sauerkraut (once), and soy sauce (twice).

Comment: The blood pressure elevation in this patient may have been related to excessive tyramine from food sources in the presence of STS therapy with the 30mg patch. However, lack of information about the timing and amounts of the above foods that were ingested preclude any definitive conclusion.

Patient 02069 was a 46 year old Caucasian female with a medical history remarkable for premature ventricular contractions (PVC's) and hypertension, which was under treatment. She was treated with STS 20mg until day 8, then 30mg until day 21, then 40mg. On day 53, she was admitted to the hospital with chest pain and increased PVC's. An ECG revealed frequent PVC's with ventricular trigeminy. No acute ST segment changes were noted. STS was stopped for one day (day 53). She was discharged on day 54 with instructions for further cardiac evaluation. STS was reduced to 30mg on day 56. She discontinued STS on day 66. A final evaluation on day 70 revealed PVC's and bigeminy.

Comment: The past history of PVC's makes it somewhat doubtful that STS played a significant role in this ECG abnormality. Nonetheless, it is possible that STS increased PVC frequency in this patient. Results of the cardiology evaluation may have been helpful in further assessing this case.

Patient 08025 was a 57 year old Caucasian male who was treated with STS, mostly at 40mg, up to day 195, when he experienced angina and presented at the emergency room. STS was discontinued and he was admitted for balloon angioplasty and stent placement for blockage of the left anterior descending coronary artery. He was released the following day and was fully recovered five days later.

Comment: In the context of the underlying coronary artery pathology, it seems unlikely that STS played any significant etiologic role in this event.

Patient 08050 was a 58 year old Black female who was titrated to STS 40mg by day 22. On day 72, she experienced two syncopal episodes which led to hospitalization for a cardiac evaluation. STS was discontinued on day 72. The

evaluation was negative and the patient was discharged on day 75. Vital sign and ECG information at the time of the syncopal episodes was not provided but, at other time points during the study, these data were unremarkable. This patient had a history of several medical problems including hypertension, high cholesterol, anemia, and hypothyroidism and was receiving multiple concomitant medications for these conditions.

Comment: STS has been associated with postural hypotension, which can produce syncope. However, this patient had been on a steady dose of STS 40mg for 50 days prior to these events, making it doubtful that STS-induced hypotension was the cause of the syncopal episodes.

Patient 11113 was a 56 year old Caucasian male who began STS 20mg with an increase to 30mg on day 8. On day 11, he was seen in the emergency room for shortness of breath. Pneumonia was diagnosed and he was sent home. On day 13, he experienced hemoptysis and returned to the emergency room. He was admitted with a diagnosis of pulmonary embolism and started on intravenous heparin. The event was reported as resolved on day 21 and the patient was discharged on Coumadin. STS was discontinued on day 22. His past medical history was unremarkable.

Comment: Given the short period of STS treatment before the onset of pulmonary embolism, it seems unlikely that STS had an etiologic role in this event.

Patient 13028 was a 37 year old Caucasian male who was titrated to an STS dose of 40mg by day 22. On day 294, the patient lost consciousness for less than 60 seconds and was taken to the emergency room. At that time, his blood pressure was found to be elevated (blood pressure values were not provided). A cardiac stress test was performed and was positive. He underwent an angioplasty for a 35% blockage. STS was continued during hospitalization. He was discharged on day 295 in stable condition on clonidine, atorvastatin, and warfarin. STS was discontinued on day 378. His medical history was remarkable for angioplasty for coronary blockage about 2 years prior to participation in this study, hypertension, and hyperlipidemia.

Comment: Although it seems unlikely that STS played a role in this patient's cardiac pathology, it may have played a part in the elevated blood pressure observed on

presentation in the emergency room. Blood pressure readings several days before and after this event were unremarkable but, as noted above, the reading in the emergency room was not provided. This patient's dietary survey covering the period of this event was remarkable for the ingestion of several items which, in the presence of an MAOI, might produce a blood pressure increase: beef liver (eaten once), chicken liver (twice), smoked fish (twice), and beer (five times). Although this information does suggest the possibility of a tyramine reaction, in the absence of data regarding the amount and timing of these ingestions, a definitive conclusion is not possible.

c. Adverse Events Leading to Dropout

In studies P0158 and P0204, there were six and 142 patients, respectively, who dropped out due to adverse experiences during the above time periods. In study P0204, five of the events leading to dropout were considered serious and were addressed in the above section.³ The remaining 137 dropouts from that study and the six dropouts from study P0158 are listed in Appendix 2 to this review.

Narrative summaries and, in some cases, Case Report Forms, for several patients were examined by the undersigned.⁴ Cases were selected for review based on clinically important adverse events possibly related to selegiline (e.g., potential occurrences of acute blood pressure elevation with STS) or the need to clarify the nature of the adverse experience (e.g., dropout due to "abnormal ECG"). All were from study P0204. Of the cases reviewed, the following are felt to merit some discussion.

Patient 03035 was a 45 year old Caucasian male who received STS 20mg for six days then 30mg. STS was discontinued on day 17. On day 18, he developed facial edema, throat constriction, cough, and hemoptysis. These events resolved on day 20.

Patient 04032 was a 36 year old Hispanic female who took STS 20mg for 10 days then 30mg. On day 16, she experienced moderate shortness of breath and discontinued treatment on day 17. On day 18, she had mild throat constriction which

³ Patient numbers 08025, 08050, 11113, 13034, and 22011.

⁴ Patient numbers 03022, 03035, 03059, 04032, 04033, 05062, 07035, 07040, 08034, 10107, 11122, 12035, 12074, 17030, 19060, and 22010.

lasted for one day. There was a history of drug allergy to codeine. Ibuprofen was the only concomitant medication.

Patient 04033 was a 23 year old Caucasian female who started STS 20mg. She experienced moderate itching (generalized urticaria) on day 1 and discontinued study drug on day 4. The itching resolved on day 7. There was a history of drug allergies to codeine and morphine. The only concomitant medication taken was nasal decongestants.

Comment: The above three cases are felt to represent possible or probable occurrences of an allergic reaction to STS treatment. In two of the three cases, there was a history of codeine allergy.

Patient 05062 was a 28 year old Black female who took STS 20mg for eight days, then 30mg until day 20, then 40mg. Beginning on day 89, she experienced psychosis (not further described). STS was discontinued on day 107 and the psychosis resolved on day 126. There was no prior history of psychotic symptoms. Concomitant medication included diphenhydramine, ibuprofen, cyclobenzaprine, and paroxetine.

Patient 07040 was a 39 year old Caucasian female who took STS 20mg to day 5, then 30mg to day 19, followed by 40mg beginning on day 20. She experienced auditory hallucinations, paranoia, and hypomania on day 27. Study medication was stopped on day 31. The auditory hallucinations and paranoia resolved on day 32 and the hypomania resolved on day 43. The patient had a history of irritability, insomnia, and vertigo. Concomitant medication included acetaminophen, diphenhydramine, and hydrocortisone cream.

Patient 12074 was a 55 year old Caucasian female who took STS 20mg for 10 days then 30mg beginning on day 11. She developed delusional thoughts on day 8. On day 19, she discontinued STS due to delusional thinking and drowsiness. The delusional thinking had resolved by day 21. Her past history was remarkable for hypothyroidism, migraine headaches, osteoarthritis, and insomnia. Concomitant medications included thyroid replacement and celecoxib.

Comment: The above three reports suggest an association between STS treatment and psychotic symptoms. In all three patients, the absence of a previous history of psychotic

symptoms and, in the latter two cases, fairly rapid resolution after stopping STS therapy are remarkable. Onset in two of the three cases was within 3-4 weeks of starting STS treatment. A role for STS in these events is biologically plausible based on the enhancing effect of selegiline on the dopaminergic system.

To further explore this potential risk, the adverse event dataset for the pool of the five short-term, placebo-controlled studies in the EMSAM development program was examined by the undersigned reviewer ($N_{\text{STS}} = 817$, $N_{\text{placebo}} = 668$).⁵ All verbatim terms were examined to identify those that could represent double-blind treatment-emergent psychotic symptoms (e.g., delusions, hallucinations, and paranoia). Only one such event was identified: Patient E113/00808 experienced paranoia during treatment with placebo. A broader examination revealed two reports of paranoid reactions during open-label STS treatment.⁶ Overall, although an association between EMSAM and psychotic symptomatology appears unlikely, this possibility cannot be entirely ruled out given the above cases and a plausible mechanism.

Patient 12035 was a 38 year old Caucasian female who experienced headache and stiff neck beginning on day 3 of treatment with STS 20mg. She discontinued treatment after day 6 and these events resolved by day 8. Screening, baseline, and day 8 blood pressure values were unremarkable.

Comment: Blood pressure readings during these events were not performed. Thus, although headache and stiff neck have been reported during MAOI-associated hypertensive crises, any blood pressure elevation in this patient at the time of these symptoms would have been undetected. It is noted that this patient did consume some cheeses during this time frame that might provoke a hypertensive crisis in the presence of an MAOI (cheddar, mozzarella, and parmesan cheeses). However, lack of information about the amounts ingested and the timing of the ingestions in addition to the lack of blood pressure data do not permit any definitive conclusions about the nature of these events.

⁵ AE.xpt file submitted on 8-7-03.

⁶ Patients 9806/17010 and E113/01119.

d. Common Adverse Events

Since the studies encompassed by this update were not placebo-controlled and were significantly longer in duration than other placebo-controlled studies in the STS development program, a comparison of adverse event incidence between these trials and the placebo-controlled study pool is not tenable and will not be addressed here.

D. Labeling

Based on the labeling attached to our 1-30-04 approvable letter, Somerset has proposed a number of changes. Clinical comments on the sponsor's proposed revisions to our approvable labeling are offered below.

I will discuss a major concern that pertains to several sections of labeling first: the need for tyramine dietary restrictions with EMSAM.

Tyramine Dietary Restrictions

We had proposed that all three EMSAM strengths would require dietary tyramine restrictions. The sponsor has modified our proposed labeling to indicate that the EMSAM 20mg patch produces preferential inhibition of MAO-B activity (versus MAO-A) and therefore dietary tyramine restrictions are not needed at this dose. At this time, Somerset does agree that tyramine restrictions with the 30mg and 40mg patches are warranted due to limited safety data at those doses.

In my previous review, I asserted that tyramine dietary restrictions should be labeled for EMSAM. That position was based in large part on data at the high dose (40mg). The question of whether restrictions were necessary for the lowest labeled dose (20mg) was not specifically addressed in that review. Following is a presentation of the sponsor's position followed by my thoughts on this specific question.

Somerset Position

Somerset provides no new clinical data directly relevant to the need for a tyramine restricted diet. In support of their position that the 20mg patch does not require tyramine restrictions, Somerset advances the following arguments.

Most Phase 1 tyramine studies were conducted using the 20mg patch and demonstrated tyramine sensitivity factors (TSF's)

of 1.8 to 2.8 (i.e., approximately a 2- to 3-fold increase in pressor sensitivity to orally administered tyramine). In these studies, the average oral tyramine dose to produce a sustained increase in systolic blood pressure of ≥ 30 mmHg (TYR30) was ≥ 200 mg in fasted subjects. This would be equivalent to over 400mg of tyramine in fed subjects since food appears to reduce the bioavailability of tyramine by a factor of about two.¹⁵ Since it is currently thought that a meal containing tyramine-rich foods might contain up to 40mg of tyramine, a safety factor of 10-fold was felt to be shown.

In particular, Somerset feels that the following Phase 1 findings support their position:

- 1) In study P9802, 12 subjects consumed a large tyramine load consisting mostly of aged cheeses (estimated tyramine content up to 320mg). Vital signs were monitored after these meals at baseline and after reaching steady-state with STS. No subject reached the pressor endpoint after STS 20mg although one subject did reach the endpoint after the tyramine meal alone at baseline.
- 2) Compared to oral selegiline (Eldepryl), STS 20mg produced a nearly identical tyramine sensitivity (TSF's of 1.70 ± 0.84 and 1.75 ± 0.54 , respectively). Eldepryl has been safely marketed since 1989 without dietary restrictions. [*Comment*: However, it should be noted that a few cases of hypertensive reactions with ingestion of tyramine-containing foods have been reported in patients taking recommended doses of oral selegiline (see the WARNINGS section of Eldepryl labeling). Also, it should be noted that the selegiline AUC is much higher when delivered via STS compared to oral administration.]
- 3) Compared with tranylcypromine, an MAOI which requires dietary restrictions, STS 20mg demonstrated a TSF at least 20 times smaller. [*Comment*: This ratio is based on data following 10 days of STS treatment. Following 33 days of STS exposure, the ratio is closer to 14.]

As further support for their position, Somerset points out that, with the exception of the first Phase 3 study (E106-95B), all of the EMSAM studies in depressed patients have been conducted without dietary restrictions and no cases of hypertensive crisis were reported. This data encompasses

¹⁵ See VanDenBerg C, et al. Tyramine Pharmacokinetics and Reduced Bioavailability with Food. J Clin Pharmacol 2003;43:604-609. Also, see the results of study P0201 as described in my 12-16-03 clinical review.

over 2,500 depressed patients exposed to the 20mg patch and an additional 750 patients exposed to the 30mg and 40mg patches.

To further explore for any unreported occurrences of acute hypertensive reactions, the sponsor searched their Phase 3 database electronically for reports of any of 12 adverse experiences that could be associated with a hypertensive episode.¹⁶ Then, a second level review was performed by the Somerset medical team on 178 patients who met certain criteria. No events judged to be hypertensive reactions were discovered.

Similar reviews on the Phase 3 Alzheimer's studies (with the 20mg patch) and Parkinson's disease studies (with the 15mg patch) likewise produced no cases.

Somerset states that they have continued to monitor ongoing studies for any hypertensive events that might represent a dietary-induced hypertensive crisis. This ongoing review has not revealed any evidence of a dietary-induced hypertensive crisis.

Comment: The absence of reports of hypertensive reactions in clinical trials with the 20mg patch is only partially reassuring. Quantities of tyramine ingested by patients in these trials were not documented in sufficient detail to evaluate the adequacy of the tyramine challenge experienced by these patients. Also, blood pressure monitoring may not have been adequate to detect significant blood pressure changes. As noted by one of the early researchers in this field, some subjects may be asymptomatic while experiencing a substantial blood pressure elevation.¹⁷

FDA Reviewer's Position

Somerset's arguments for not requiring dietary restrictions at the 20mg dose of EMSAM have some merit and cannot be dismissed off-hand. As they correctly point out, following our review of their original submission which provided for use of only the 20mg patch, we were inclined to agree that dietary restrictions were not necessary at that dose.¹⁸

¹⁶ A detailed description of the methodology and results of this search was submitted in the ISS Amendment (pages 179-184) of the 7-31-03 NA response.

¹⁷ Blackwell B, et al. Hypertensive Interactions Between Monoamine Oxidase Inhibitors and Foodstuffs. *Br J Psychiat* 1967;113:349-365.

¹⁸ See our 3-25-02 NA letter.

Although we expressed a concern at that time that the pressor dose might decline over time with chronic EMSAM use, that concern has been addressed by a subsequent study which was submitted as part of their 7-31-03 NA response (study P0201). That investigation showed a decline in pressor dose over the first 30 days of treatment with the 40mg patch but little change after 60 and 90 days of treatment.

For the convenience of the reader, Table 1 below summarizes previously reviewed tyramine challenge data with STS.

TABLE 1: SUMMARY OF MEAN RESULTS FROM TYRAMINE CHALLENGE STUDIES WITH STS UNDER FASTING CONDITIONS				
Drug (N)	Dose/Duration	Baseline TYR30 (mg)	On-Drug TYR30 (mg)	TSF
STS (47)	20mg/9-10d	507±106	298±105	1.8±0.5
STS (12)	20mg/30d	483±139	204±86	2.9±1.5
STS (10)	30mg/10d	470±178	210±88	2.4±0.7
STS (12)	40mg/10d	588±117	198±98	3.5±1.3
STS (18)	40mg/30d	575±93	84±70	11.5±6.6
Oral Selegiline (21)	5mg BID/9d	529±115	357±147	1.7±0.8
Tranlycypromine (10)	30mg/8d	400±71	10±0	40±7.1
Fluoxetine (12)	60mg/48d	533±91	408±131	1.4±0.6

As a caveat, these data derive from a number of studies and, hence, comparisons across doses and drugs must be drawn with some caution. Nevertheless, these data do suggest the following:

- 1) a dose-response for tyramine sensitivity with STS, holding duration of treatment constant.
- 2) a time-dependency for tyramine sensitivity, as evidenced by the higher TSF values after 30 days of STS treatment versus after 9-10 days of treatment at the same dose. In study P0201, continued treatment to 60 and 90 days did not demonstrate an increase in tyramine sensitivity beyond the first 30 days of STS exposure.
- 3) the mean TSF for the 20mg patch approximates that for oral selegiline and is only slightly higher than for fluoxetine, the presumptive inactive control.
- 4) the mean TSF values for all STS doses are much smaller than that for the active control, tranlycypromine.

The latter point raises the obvious question of whether tyramine precautions are necessary with any of the three doses of STS. Based on my review of tyramine pressor doses with the 40mg patch from study P0201, there is an

inadequate safety margin at that dose to justify omission of tyramine restrictions, in my judgement.¹⁹ The mean pressor dose after 30 days of STS treatment was 84mg, with a range of 25-200mg. The lower end of that range only slightly exceeds the amount of tyramine that might be ingested in food or beverages (40mg) after adjusting for the fact that this was under fasting conditions (i.e., 50mg). Data under fed conditions in that study indicated a mean pressor dose of 172mg, with a range of 75-300mg. The margin of safety at the lowest pressor dose (75mg) is not large and the high-fat meal ingested in this trial may, in fact, have underestimated the exposure to tyramine in a typical meal.

Also, in agreement with the sponsor, I am not inclined to recommend approval of the 30mg patch without dietary restrictions due to limited experience with that dose to date.

With regard to the 20mg patch, these data lend some support to the sponsor's proposal. However, Somerset's arguments tend to focus on mean data. Consideration of a potentially significant hazard mandates deliberation of not just how the average patient may be impacted but whether a small subset of susceptible patients may be placed at undue risk. That is, attention must also be paid to the range of responses and the need for an adequate safety buffer when data are quite variable. Along this line, the one reservation I do have about approving the 20mg patch without tyramine restrictions is the variability in tyramine sensitivity. The following points illustrate my concern.

Of the above reviewed studies, the most relevant here is study P0045, which examined tyramine pressor doses under fasted conditions following approximately 30 days of treatment with the STS 20mg patch in 12 healthy males with a mean age of 32 years (range 19-50 years). As indicated in Table 1, the mean pressor dose after STS treatment was 204mg and the mean TSF was 2.9. The modal pressor dose in this study was 200mg (in eight subjects). But the range of pressor doses was 50-400mg, with one subject attaining a pressor response with 50mg of tyramine and a second with 100mg of tyramine. TSF values in these subjects were 6.0 and 5.5, respectively. An examination of the selegiline

¹⁹ See my 12-16-03 clinical review.

plasma levels around the time of the tyramine challenge does not suggest that these increases in tyramine sensitivity were related to outlying plasma levels of drug. Given that the tyramine challenge was performed under fasted conditions and one would not generally expect a dietary ingestion of greater than 40mg of tyramine, neither pressor dose is alarming. On the other hand, the relatively high TSF's in these subjects do indicate substantial inhibition of MAO-A. Also, it must be borne in mind that the algorithms for determining pressor doses in tyramine challenge studies may substantially overestimate the actual minimum pressor dose in some cases; a margin of safety should be demanded as a buffer for this source of error. These considerations raise the question of whether a small proportion of patients in the target population may experience hypertensive reactions with the 20mg patch without dietary restrictions.

As further evidence of variability in tyramine sensitivity, consider the difference in pressor doses between the two baseline periods, about one week apart, for each subject in study P0045. The protocol for determining pressor dose during these periods in effect rounded the actual pressor dose up to the nearest 100mg. This factor alone can produce appreciable variability. Still, of the 12 subjects in this trial, three had a difference of 200mg and two had a difference of 300mg. Due to the rounding process, it is not possible to estimate the difference in actual pressor doses but obviously a recorded difference of 200mg must represent an actual change of at least 100mg in the pressor dose and a recorded difference of 300mg must represent an actual change of at least 200mg. This degree of variability over a one week interval in a small number of untreated, healthy subjects points to the need for insisting on a wide margin of safety in deciding this question.

In the above study, the sources of variability are unknown. Other sources may be identifiable. One specific source in the target population may be related to altered pharmacokinetics in older females. An analysis of STS pharmacokinetic data by age revealed a 62.5% increase in selegiline exposure in females from age 20 to age 70 years (about a 1.25% increase per year) and a 25% increase in males (about a 0.5% increase per year).²⁰ In this

²⁰ See the 1-14-04 biopharmaceutics review (page 90).

submission, Somerset has provided an analysis of the effect of age on selegiline plasma concentrations which purportedly shows no effect of age on steady-state selegiline levels in depressed patients up to age 87 years, regardless of gender. This analysis is currently under review by the biopharmaceutics reviewer, Dr. Ronald Kavanagh. But, if the sponsor's position is not accepted and some elderly female patients are expected to be exposed to higher levels of selegiline, then such patients treated with the 20mg patch may resemble younger patients treated with the 30mg patch in terms of tyramine sensitivity and could be at risk for a hypertensive reaction in the absence of tyramine restrictions.

Another possible specific source of variability is an interaction with agents that elevate selegiline levels. One particular concern is a possible effect of oral contraceptives on selegiline levels, as reported by Laine and colleagues.²¹ This Finnish study compared selegiline and desmethylselegiline pharmacokinetics after oral selegiline administration (5, 10, 20, and 40mg) in eight female subjects, four of whom were taking concomitant oral contraceptives. The bioavailability of selegiline was drastically increased (20-fold) in those subjects using oral contraceptives, with marked increases in both Cmax and AUC. This study is currently under review by Dr. Andre Jackson of the biopharmaceutics staff and a decision about labeling this information will be made following completion of his review. Since females using oral contraceptives are likely to comprise a sizeable portion of the target population for EMSAM, lack of tyramine restrictions with the low dose patch would present an obvious hazard to such patients if the results of this study are borne out. Of course, it may be prudent to simply contraindicate the use of EMSAM (and perhaps other selegiline products) with oral contraceptives.

In conclusion, given the large variability in tyramine sensitivity and the need for a wide safety margin, I am not persuaded that the risk associated with tyramine ingestion with the 20mg patch is sufficiently distinct from that with the 30mg and 40mg patches to warrant different safety precautions. For this reason alone, I do not advocate approval of the 20mg EMSAM patch without tyramine

²¹ Laine K, et al. Dose linearity study of selegiline pharmacokinetics after oral administration: evidence for strong drug interaction with female sex steroids. *Br J Clin Pharmacol.* 1999;47:249-254.

restrictions and recommend that the FDA proposed text for labeling this issue remain.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The sponsor has added language to this section to indicate that the EMSAM 20mg patch produces preferential inhibition of MAO activity in the brain compared to peripheral tissues and therefore dietary tyramine restrictions are not needed at this dose. At this time, Somerset does agree to tyramine restrictions for the 30mg and 40mg patches due to limited safety data at those doses.

In the end, if tyramine restrictions are required for all three patch strengths, the FDA proposed language for this and other pertinent sections of labeling should stand.

III. Conclusions and Recommendations

Sufficient evidence has been previously submitted to demonstrate the efficacy of EMSAM in the treatment of depression.²³ Before we grant final approval to this application, there are a number of safety-related issues that must be resolved, many of which are dependent on reviews from other disciplines that are still in progress:

²³ See my clinical reviews dated 2-28-02 and 12-16-03.

Gregory M. Dubitsky, M.D.
August 19, 2005

cc: NDA #21-336
NDA #21-708
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PAndreason
/DBates

APPENDIX 1	
PATIENTS WITH SERIOUS ADVERSE EVENTS	
Study/Patient	Serious Adverse Event(s)
Study P0158	
10094	Chest pain (musculoskeletal)
Study P0204	
02064	Chest pain/Elevated blood pressure
02069	Chest pain/Increased PVC's
04041	Colon cancer
05016	Fall
07043	Chest wall contusion/Neck strain
08025	Angina
08050	Syncopal episodes
11113	Pulmonary embolism
13028	Loss of consciousness/Elevated BP
13034	Suicidal ideation
14019	Kidney stones
17040	Laminectomy and bone graft
19043	Gallbladder removal
21047	Motor vehicle accident
22011	Fall/Fractured hip/Hip replacement
22022	Suicidal ideation
Study P0043	
CU021	Lumpectomy

APPENDIX 2: DROPOUTS DUE TO ADVERSE EVENTS	
Study/Patient	Adverse Event(s) Leading To Dropout
Study P0158	
10058	Insomnia
10096	Insomnia/Impotence
10108	Decreased concentration/Memory loss
32009	Constipation/Restlessness/Hot flashes
32014	Insomnia
33020	Application site reaction
Study P0204	
02010	Bilateral breast lumps
02012	Application site reaction
02013	Increased anxiety/Agitation
02023	Worsening asthma
02028	Nocturnal diaphoresis/Hot flashes/ Palpitations
02045 ²⁵	Anorgasmy
02056	Application site reaction
02061	Application site reaction
02063	Dizziness
03014	Anxiety/Restlessness
03022	Exacerbation of hypertension
03026	Insomnia
03032	Application site reaction
03035	Facial edema/Throat constriction/ Cough/Hemoptysis
03038	Dizziness/Orthostatic hypotension
03041	Nervous skin excoriation
03059	Abnormal ECG
03064	Application site reaction
03067	Nausea/Stomach upset/Dizziness
03069	Heart palpitations
04032	Shortness of breath
04033	Generalized urticaria
04040	Application site reaction
04051	Dizziness
05036	Application site reaction
05044	Pedal edema/Dry mouth/Dry cough/Bruising/ Application site reaction
05058	Moderate weight gain
05061	Hypomania

²⁵ A Narrative Summary was not provided for this patient. Information was derived from the Case Report Form.

APPENDIX 2: DROPOUTS DUE TO ADVERSE EVENTS	
Study/Patient	Adverse Event(s) Leading To Dropout
05062	Psychosis
05070	Application site reaction
05074	Orthostatic hypotension
06012	Dizziness/Blurred vision
06017	Application site reaction
06019	Sexual dysfunction/Insomnia
07003	Insomnia
07005	Irritability
07013	Increased suicidality/Rapid cycling bipolar-like state
07014	Application site reaction
07016	Lightheadedness/Dizziness/Orthostatic hypotension
07018	Insomnia/Lightheadedness/Dizziness
07019	Application site reaction
07022	Migraine syndrome
07030	Hypomania
07032	Application site reaction
07035	Elevated AST/ALT/LDH
07039	Stomach pain
07040	Application site reaction/Hallucinations/Paranoia/Hypomania
07041	Application site reaction/Impaired concentration/Impaired memory/Tinnitus/Night sweats/Vivid dreams/Dizziness/Nausea
07044	Irritability
07048	Pregnancy
07053	Insomnia
08014	Application site reaction
08023	Induction of mania
08026	Rash
08034	Elevated glucose/ALT/AST
08041	Insomnia/Orthostatic dizziness
08042	Application site reaction
08043	Application site reaction
08044	Headache/Stomachache
08049	Insomnia/Tinnitus/Decreased appetite
10060	Application site reaction
10080	Application site reaction
10088	Nervousness/Palpitations
10092	Headache/Insomnia
10094	Hip pain
10099	Headache/Increased appetite

APPENDIX 2: DROPOUTS DUE TO ADVERSE EVENTS	
Study/Patient	Adverse Event(s) Leading To Dropout
10107	Congestive heart failure/Edema/Insomnia
10110	Dizziness
11013	Worsening impotence
11022	Insomnia
11026	Nausea
11029	Application site reaction
11055	Insomnia
11060	Decreased libido/Confusion/Dizziness/ Drowsiness
11070	Insomnia/Nausea/Decreased appetite
11079	Application site reaction
11089	Agitation/Persistent insomnia
11098	Application site reaction
11106	Insomnia/Dry mouth/Anxiety
11108	Application site reaction
11109	Headaches/Racing thoughts/Obsessive compulsive behavior
11114	Acute lower back strain
11122	Increased blood pressure
12021	Broken capillaries on face
12022	Lower back pain
12024	Decreased libido
12035	Headache/Stiff neck
12036	Insomnia
12038	Insomnia/Weight gain
12050	Headaches/Indigestion/Constipation
12054	Hip pain
12057	Severe sweating/agitation
12058	Insomnia
12063	Application site reaction
12064	Insomnia/Irritability
12065	Violent thoughts/Hypomania
12067	Metallic taste
12069	Drowsiness
12071	Irritability/Insomnia/Manic symptoms
12074	Delusional thoughts/Drowsiness
12077	Dizziness
13017	Application site reaction
13055	Dizziness
13059	Swollen lip
14017	Flu-like symptoms
15016	Insomnia

APPENDIX 2: DROPOUTS DUE TO ADVERSE EVENTS	
Study/Patient	Adverse Event(s) Leading To Dropout
15017	Anxiety
15019	Application site reaction
15037	Application site reaction
15048	Irritability
17030	Dizziness/Pressure in head
17031	Application site reaction
17034	Application site reaction
17036	Alcoholism
17041	Irritability
17043	Agitation
17048	Insomnia
19022	Application site reaction
19045	Hypersomnia/Dizziness
19054	Lightheadedness/Dizziness/Dry Mouth/ Sleeplessness/Nausea/Sharp abdominal pain
19059	Sleeplessness
19060	Auditory hallucinations
19071	Sleep loss
21016	Pregnancy
21017	Application site reaction
21025	Insomnia
21026	Application site reaction
21035	Nausea
21041	Dizziness
21042	Hypomania
21053	Application site reaction
21057	Insomnia
21059	Insomnia
22005	Insomnia/Suicidal ideation
22008	Insomnia/Irritability/Headache/Vertigo/ Hot flashes/Heart palpitations/Anorgasmia/ Suicidal ideation/Hypotension
22010	Dizziness/Headache
22015	Anxiety/Insomnia/Erectile dysfunction/ Orthostasis

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this page is the manifestation of the electronic signature.**

/s/

Greg Dubitsky
8/19/2005 05:05:07 PM
MEDICAL OFFICER

Thomas Laughren
9/21/2005 07:28:37 AM
MEDICAL OFFICER
We are bringing these NDAs to the PDAC for
discussion of the dietary restriction issue--TPL