

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-336/21-708

MEDICAL REVIEW(S)

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 26, 2006

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for Approval Action for
Emsam (selegiline transdermal system [STS])

TO: File NDAs 21-336 and 21-708
[**Note:** This memo should be filed with the 5-26-05 response to our 1-30-04
approvable letter.]

BACKGROUND

Selegiline transdermal system [STS] is a patch formulation of selegiline, a monoamine oxidase inhibitor (MAOI) that is currently marketed as Eldepryl (an immediate release capsule for oral administration) as an adjunctive treatment for Parkinson's disease. It is being proposed for the treatment of depression, in a dose range of 20 to 40 mg/day (dosage strengths are 20, 30, and 40 mg patches, which deliver approximately 6, 9, and 12 mg/24 hours, respectively). MAO exists as two isoenzymes, A and B, and these isoenzymes have a role in the catabolism of neurotransmitter amines such as NE, DA, and 5HT. At low concentrations, selegiline is selective for MAO B, but at higher concentrations, it inhibits both A and B. In fact, inhibition of both isoenzymes may be necessary for the antidepressant action of STS, since it was positive in the forced swim test (an animal model for depression) only at doses that inhibited both isoenzymes. Since MAO in the gut wall is also important in the catabolism of certain dietary amines (e.g., tyramine), one concern about MAOIs is their potential to inhibit gut MAO-A, resulting in the "cheese reaction." However, the STS formulation avoids exposure of gut wall MAO-A to selegiline, and "cheese reactions" have not been observed with STS, even without the dietary restrictions that need to be observed with orally administered, nonselective MAOIs. Thus, STS might be expected to have the advantage over other MAOI's marketed in the US for depression (phenelzine, tranylcypromine, and isocarboxizide) of not having the same potential for the "cheese reaction."

The original NDA for STS was submitted 5-24-01, and we issued a nonapprovable letter on 3-25-02 (Note: See my 3-15-02 memo to the file for a more detailed discussion regarding this original submission and our nonapprovable action). The deficiency that was the basis for the NA action was a failure to provide sufficient evidence of effectiveness. The NDA had included efficacy data for 4

short-term trials, and we were in agreement on the interpretation for 3 of these trials. In particular, we agreed that study S9303-E106-96B was a positive trial, and that studies S9303-E113-98B and S9303-E114-98B were negative trials. We were not in agreement about the interpretation of study S9303-P9804. We did not consider this a positive study, based on the protocol specified analysis. Since, in all 4 studies, the highest dose or the only dose was 20 mg, we recommended in our NA letter that the sponsor explore dose response for effectiveness in future studies. In addition to this critical deficiency regarding effectiveness data, we noted in the letter several other deficiencies that needed to be addressed. The NDA was resubmitted on 7-31-03, and included results of both the new short-term efficacy trial and also the randomized withdrawal trial. It also responded to the other issues noted in the nonapprovable letter. We reviewed this response and issued an approvable letter 1-30-04. This letter included several deficiencies:

-Chemistry:

We asked for a _____ for determining the _____ of selegiline.

impurities: We raised concern about 5 impurities _____ that are suspected mutagens and asked that these either be reduced to no greater than _____ or that they do studies to show a lack of mutagenicity.

-Pharm/Tox:

-2 year mouse carcinogenicity study: We asked for a 2 year mouse carcinogenicity study, however, subsequently agreed that this could be done in phase 4.

-In vivo micronucleus assay: We asked for either justification for the oral route in the in vivo assay, or conduct of another in vivo study by a route that would ensure higher selegiline exposures.

-OCPB:

-Dissolution specifications: We proposed dissolution specifications.

-Phase 4 commitments: We asked the sponsor to commit to conducting phase 4 studies to better establish the adhesive properties of the patch, its dermal tolerability, and its performance in the elderly.

-Clinical:

-Safety Update: We asked the sponsor for a safety update as part of their response to our 1-30-04 AE letter.

-Safety Issues Needing Resolution: We had identified a number of safety issues for which there was still disagreement between FDA and the sponsor regarding how to characterize these issues in labeling. The sponsor agreed with our proposed solutions for some of these, but not others, and following are the more prominent issues that needed resolution as part of this review cycle:

-Potential for Hypertensive (Cheese) Reactions: In our 1-30-04 AE letter, we had proposed labeling that included dietary restrictions for all 3 Emsam strengths.

-Concern about Melanoma: This concern was actually raised in the context of the review of _____

Given the potential signal for the other drug, we asked Somerset to provide data pertinent to melanoma both for the selegiline patch and for the oral selegiline product during the review cycle for this 5-26-05 response to the AE letter.

-Name and Packaging:

-Name: We informed Somerset that their proposed name, Emsam, was acceptable, however, we also noted that the name would need to be reconsidered prior to final approval.

-Packaging Advice: We also conveyed advice about the patch label, pouch label, and carton labeling.

-Regulatory Update/Foreign Labeling:

-Regulatory Update: We asked for a foreign regulatory update.

-Foreign Labeling: We asked for foreign labeling.

-World Literature Update: We asked for a literature update.

-Labeling: We proposed draft labeling that included a number of changes to the sponsor's proposed label.

We decided to take selegiline transdermal system (STS) to the Psychopharmacological Drugs Advisory Committee (PDAC) for a discussion of the sponsor's proposal to market the 20 mg strength without a requirement for dietary restrictions (but dietary restrictions would be required for the 30 and 40 mg strengths).

RESPONSE TO APPROVABLE LETTER

-Chemistry:

- The sponsor adequately responded to this deficiency.

- Impurities: The sponsor worked with CMC staff to lower the levels of the 5 impurities to an acceptable level, and they provided arguments, based on published literature, to make a case that the levels present are not a concern. Dr. Fossom has accepted their arguments, but does recommend that the patch not be administered to irritated skin (proposed labeling includes this recommendation).

-Pharm/Tox:

-2 year mouse carcinogenicity study: The sponsor has agreed to conduct a 2-year mouse study using the dermal route as a ph 4 commitment.

-In vivo micronucleus assay: The sponsor has also agreed to conduct an in vivo micronucleus assay using the dermal route as a ph 4 commitment.

-OCPB:

-Dissolution specifications: The sponsor has accepted our proposed dissolution specifications.

-Phase 4 commitments:

-Study of Adhesive Properties of Patch: The sponsor has agreed to conduct such a study. They agreed to submit a protocol within 3 months of approval, and a final study report within 9 months of agreement on the protocol.

-Study of Dermal Tolerability of Patch: The sponsor has agreed to conduct such a study. They agreed to submit a protocol within 3 months of approval, and a final study report within 9 months of agreement on the protocol.

-Performance in Elderly: An earlier analysis of pk data by age suggested increases with age, however, this correlation appears to have been based on an erroneous assumption about sampling times. The sponsor provided additional pop pk data in elderly patients in the 5-26-05 response, however, their finding of no age effect is difficult to interpret because of inadequate numbers of elderly patients and uncertainty about sampling times. In addition, the sponsor had eliminated, as chance variants, excessive levels in 3 patients, which OCPB feels is questionable. Thus, OCPB feels that additional data in the elderly are still needed. We have discussed this with the sponsor, and they have committed to gathering additional data in ph 4. They agreed to submit a protocol within 3 months of approval, and a final study report within 9 months of agreement on the protocol.

-Clinical:

-Safety Update: The safety update included additional data for 3 studies (all open label) that were ongoing at the time of the 1-30-04 AE letter. There were no deaths among these additional open label patients, however, there were 18 SAEs. Dr. Dubitsky reviewed these data, and commented on 6 of these SAEs that he felt needed discussion. These patients experienced: cardiac events (1 with PVCs and hypertension; 2 with coronary artery blockage); hypertension (1 patient); syncopal episodes (1 patient); and, pneumonia (1 patient). Two of these patients had at some time eaten foods that have been linked to hypertensive reactions with oral MAOIs, however, there was insufficient information for either of these cases to even remotely link the events in question to intake of these foods.

Dr. Dubitsky also commented on 7 patients who dropped out for various adverse events while taking Emsam, out of a total of 148 adverse dropouts listed in the safety update. He felt that 3 might represent allergic reactions to Emsam. He felt that 3 others might represent psychotic symptoms possibly precipitated by Emsam. Finally, he reviewed a patient who experienced headache and stiff neck while taking Emsam. No blood pressure data were available. She had ingested some foods that have been associated with cheese reactions, however, the timing with the events in question was not specified. Thus, none of these cases, in my view, contributed to a better understanding of the adverse event profile for Emsam. However, I agree with Dr. Dubitsky that ODS might want to include allergic reactions and psychotic reactions among the events to look for postmarketing.

-Safety Issues Needing Resolution:

-Potential for Hypertensive (Cheese) Reactions:

As noted above, MAO-A in the gut wall and liver is important in the catabolism of certain dietary amines (e.g., tyramine), and a concern for MAOIs is their potential to inhibit gut MAO-A, resulting in the "cheese reaction." However, the STS formulation avoids exposure of gut wall and first pass liver MAO-A to selegiline, thus, STS might be expected to have the advantage over other MAOI's marketed in the US for depression (phenelzine, tranylcypromine, and isocarboxizide) of having less potential for the "cheese reaction." Somerset has 2 sources of evidence that they believe support the view that dietary restrictions of the type imposed on orally administered nonselective MAOIs are not needed for the 20 mg patch. They have accepted the need for these restrictions for the 30 and 40 mg strengths.

-First, most of their phase 3 experience with STS was obtained without any dietary restrictions (n=2503, including 1606 at 20 mg, and 947 at 30 or 40 mg), and there were no hypertensive crises reported.

-Second, they conducted a series of tyramine challenge studies (n=214 healthy subjects) to demonstrate what they feel is a substantial safety margin for the 20 mg strength. Key among these studies were the following:

-A crossover study (n=13) assessed TYR30 for STS 20 vs oral selegiline 5 mg bid, for 10 days, fasting; mean pressor doses were 338 mg for STS and 385 for oral selegiline. These represent TSFs of about 2 for both.

-A crossover study (n=10) assessed TYR30 for STS 20 vs oral tranlycypromine 30 mg/day, for 10 days, fasting; mean pressor doses were 270 mg for STS and 10 for oral tranlycypromine.

-A crossover study (n=13) assessed TYR30 for STS 20, after 9 and 33 days, fasting; mean pressor doses were 292 and 204, respectively. The lowest pressor dose was 50 mg, in a subject in the 33 day group.

-Pressor doses were studied in n=11 subjects with STS 40 after 30, 60, and 90 days, fasting; mean pressor doses were 95, 72, and 88 mg, respectively. The lowest pressor dose was 25 mg, in a subject at 30 days. Eight subjects with a mean pressor dose of 64 mg at 90 days were given tyramine with food, and had a mean pressor dose of 172 mg (2.7 times the pressor dose fasting).

-In summary, both STS 20 mg and oral selegiline 5 mg bid have equal TSFs (about 2), compared to a TSF of 40 for tranlycypromine 30 mg. Tyramine challenge studies reveal a safety margin for STS 20 mg of about 10 when tyramine is given with food (the only relevant condition, since the concern is a tyramine-rich meal), given the estimated maximum tyramine content in a tyramine-rich meal of 40 mg.

-Additional arguments in favor of permitting the 20 mg strength to be marketed without dietary restrictions include the following:

-The fed state is the only relevant condition, and the lowest pressor dose for STS 20 in the fed state would be 125 mg (an extrapolation), a level 3 times higher than the highest imaginable high-tyramine meal.

-A pressor dose is not an indication of a hypertensive crisis, but rather, a rise of 30 mm Hg; this is a blood pressure change that normally occurs multiple times throughout the day. Thus, while this clearly indicates a change in tyramine sensitivity, it does not necessarily indicate a clinically relevant change.

-STS 20 is completely indistinguishable from oral selegiline 5 mg bid with regard to tyramine sensitivity, a dose that has been used for 16 years without evidence of hypertensive crises. Dr. Dubitsky notes that there have been a few reports of such crises, however, as revealed at the PDAC meeting 10-26-05 to discuss this issue, for 3 of the 4 reported cases, there were far more plausible alternative explanations. There was insufficient information in the 4th case to conclude anything. I have discussed this issue with the Neurology Division, and they have assured me that they do not consider this a concern for oral selegiline at the 5 mg bid dose level,

-Name and Packaging:

-Name: There is a possibility of confusion with the name of another drug under development. However, EMSAM will be approved first, and thus has priority over the other product.

-Packaging Advice: ODS had several suggestions for packaging that will be included in the AP letter.

-Regulatory Update/Foreign Labeling:

-Regulatory Update:

(/ / / / / / / / /)

-Foreign Labeling: Emsam is not yet marketed anywhere.

-World Literature Update: The sponsor conducted a literature update and stated that, with the exception of 2 papers, their search revealed no new potential adverse effects. One exception was a French paper that reported mouth ulcerations with a sublingual form of selegiline. The other was a Finnish paper suggesting markedly elevated selegiline levels in patients with liver disease and in patients with renal disease given oral selegiline (This paper is discussed below under "Misc Issues).

-Labeling: We reached agreement with the sponsor on the labeling and medguide as of 2-17-06.

-Miscellaneous Issues Needing Resolution:

-Possible Effect of Altered Hepatic and Renal Function on PK: These concerns came from a published paper involving a small study with oral dosing the sponsor had included in their literature review (Anttila, et al). This paper was reviewed by OCPB and they concluded the hepatic findings, even if real, were not relevant to Emsam because it bypasses the liver. Furthermore, the renal finding in the Anttila, et al, paper is questionable, and not consistent with an earlier study reviewed by OCPB.

-Possible Interaction with Oral Contraceptives: This concern came from a published paper involving a small study with oral dosing (Laine, et al). The sponsor argued that the finding, even if real, would not be relevant to Emsam because it bypasses the liver. Further, they provided other cogent arguments why the finding may not even be real, and also provided pop pk data from their ph 3 program that suggested no oral contraceptive interaction. OCPB agreed that the Laine study is uninterpretable, but also that the sponsor's pop pk analysis is not adequate to address the question. Dr. Dubitsky has argued against requiring an additional DDI study with OC's in ph 4, and I agree.

-Question of Potential for QT Prolongation: Late in the review, a concern was raised about a possible signal for QT prolongation coming from a program for an orally disintegrating form of selegiline. There was no signal for mean change from baseline in QTc or on outliers regarding QTc, but rather, the "signal" was the finding that the upper bound of the 95% confidence interval for the largest time-matched difference between drug and placebo exceeded 10 msec. Ultimately, however, both the Division of Neurology Products and Dr. Dubitsky agreed that this was not a true finding of concern, and I agree.

-Question of need for statement. Late in the review (2-17-06), the CMC group raised a concern about the need for such a statement in the layer. A However, the patch is sealed in a pouch containing an aluminum foil study confirmed the effectiveness of the pouch. Thus, statement is not needed in this section.

CONCLUSIONS AND RECOMMENDATIONS

I believe that Somerset has now submitted sufficient data to support the conclusion that STS is effective and acceptably safe in the treatment of MDD. We have also now reached agreement with Somerset on final language for labeling and the Medguide. Thus, I recommend that we issue the attached approval letter along with the mutually agreed upon final labeling.

cc:

Orig NDA 21-336 (Selegiline Transdermal System [STS])

HFD-130

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/s/

Thomas Laughren
2/27/2006 11:05:00 AM
MEDICAL OFFICER

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

Sponsor: Somerset Pharmaceuticals
Drug: EMSAM (Selegiline Transdermal System)
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

This application for the use of the selegiline transdermal system, or EMSAM, in the treatment of major depression was deemed to be approvable on 1-30-04. The sponsor, Somerset Pharmaceuticals, submitted a response to the approvable action on 5-26-05 and I completed a clinical review of the response on 8-19-05.¹

That review identified a number of outstanding safety-related concerns which warranted resolution before a final approval action could be taken, specifically:

1) determination _____ in elderly patients, particularly older females, based on an analysis of age effect on selegiline pharmacokinetics and a population pharmacokinetic analysis submitted by the sponsor in this response.

2) determination _____ patients with altered liver or kidney function, based in part on a published study from the sponsor's literature search.²

3) determination _____ regarding a reported interaction between selegiline and oral contraceptives, based on _____

¹ Please see that review for more detailed background information on this NDA.

² Anttila M, et al. Marked effect of liver and kidney function on the pharmacokinetics of selegiline. Clin Pharmacol Ther 2005;77:54-62.

articles from the published literature and a submission dated 8-31-05 in which the sponsor addresses this issue.³

4) an assessment of the risk for melanoma with oral selegiline based on data from the original Eldepryl NDA safety database and from the DATATOP study, a long-term in patients with Parkinson's disease which included a selegiline treatment arm. Additionally, Somerset was to provide follow-up information on skin biopsies for three patients identified in their search for occurrences of melanoma in the EMSAM safety database.

5) assessment of the genotoxicity of four — as well as a degradant impurity, in the EMSAM adhesive patch and, as appropriate, specification of limits for these entities in the patch.

6) negotiation of labeling with Somerset. The primary labeling concern was whether tyramine dietary restrictions were deemed to be necessary at the lowest patch strength (20mg). After some discussion of this question with Robert Temple, M.D., ODE I Office Director, on 9-7-05 and subsequent consultation with the sponsor, it was decided to take this issue to the Psychopharmacological Drugs Advisory Committee (PDAC). The PDAC met to consider this concern on 10-26-05.

Of note, at the above PDAC meeting, Somerset presented a proposed risk management plan to educate patients, prescribers, and pharmacists about the need to adhere to dietary restrictions with use of the two higher doses of EMSAM.

In addition, subsequent to my 8-19-05 review, a possible signal for prolongation of the QT interval on ECG was found with a product closely related to EMSAM, Zelapar (or zydis selegiline). If valid, this finding might have significant implications for the cardiac safety of EMSAM.

Finally, on 11-3-05, Somerset submitted a revised labeling proposal for our examination.

³ 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 and Palovaara S, et al. Effect of concomitant hormone replacement therapy containing estradiol and levonorgestrel on the pharmacokinetics of selegiline. *Eur J Clin Pharmacol* 2002;58:259-263.

This addendum to my 8-19-05 clinical review addresses the above issues.

II. Review of Clinical Issues

A. Effect of Age on Pharmacokinetics

A previous analysis of EMSAM 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).⁴ That analysis was based on the assumption that all samples were drawn at 24 hours post-dose. Sampling times are now known and it is clear to the biopharmaceutics reviewer, Dr. Kavanagh, that this assumption is erroneous and may have resulted in the finding of a correlation of age with selegiline exposure.⁵

Somerset has provided a population pharmacokinetic analysis of the effects of dose, age, and gender on selegiline clearance. This analysis was conducted in a Phase 1 study in males ages 55-78 years and in six Phase 2/3 studies. However, the Phase 1 investigation examined only the 20mg dose in 6 subjects and failed to provide the ages of these subjects and pharmacokinetic data. Additionally, only two of the Phase 2/3 trials included subjects older than 65 years and examined doses other than just the 20mg patch (studies 052 and 204); thus, Dr. Kavanagh's review focused on these two studies, which included doses of 20, 30, and 40mg.

No clear effect of age on selegiline clearance was found. However, this analysis was not based on an adequate number of samples from elderly patients: of 257 total samples, only 39 came from subjects ages 65-75 years and only 17 came from subjects older than 75. Thus, the finding of no effect is not surprising. Other deficiencies noted by Dr. Kavanagh were lack of metabolite information and uncertainty about sampling times relative to dosing.

One remarkable finding from Dr. Kavanagh's analysis pertained to three subjects with outlier values for selegiline concentrations (i.e., greater than three standard deviations above the mean). (These data were

⁴ See the 1-14-04 biopharmaceutics review (pages 90 and 91).

⁵ See the 11-3-05 biopharmaceutics review (page 7).

excluded from the sponsor's analysis because they were considered chance variants.) One male subject in the younger age group (18-64 years) had markedly high selegiline levels at the 20mg dose on two occasions several weeks apart. A female in the 65-75 year old group experienced high levels at both the 30mg dose and the 40mg dose. A male in the over 75 year age group had a markedly high level at the 40mg dose. The replication of high exposures in two of these three subjects indicates that these exposures were not by chance alone. The factors leading to these outlier values cannot be predicted at this time.

The high exposures in the two elderly patients is worrisome and supports the need for further study of EMSAM in the old and very old populations, as requested in our 1-30-04 approvable letter. Dr. Kavanagh does not feel that the sponsor's population pharmacokinetic analysis satisfies our approvable letter request to evaluate the performance of the selegiline transdermal patch in the elderly. He recommends that Somerset fulfill this request, as well as requests to examine dermal adhesion and tolerability, as Phase 4 Commitments, with study reports to be submitted within _____ of approval.

B. Effect of Altered Hepatic and Renal Function on PK

The sponsor's most recent literature search revealed a published open-label study from Finland by Anttila and colleagues that suggested an effect of altered liver or renal function on selegiline pharmacokinetics. This investigation compared the pharmacokinetics of oral selegiline among four parallel subject groups: 1) patients with liver disease, 2) patients receiving a drug that induces hepatic enzyme activity, 3) patients with impaired kidney function, and 4) control subjects. There were 10 subjects in each group. A single 20mg tablet of selegiline (Eldepryl) was administered after an overnight fast. Blood specimens were collected over the next 48 hours and analyzed for concentrations of serum selegiline and its main metabolites.

Compared to normals, the AUC for selegiline was, on average, 18-fold higher in patients with impaired liver function ($p < 0.05$), 23-fold lower in patients with drug-induced liver function ($p < 0.001$), and 6-fold higher in patients with impaired kidney function ($p < 0.05$). There was

large variation among individuals within each group. The authors conclude that these results suggest the need for dosage adjustment when selegiline is used in patients with altered liver or kidney function.

I discussed the relevance of this study to EMSAM with Drs. Raman Baweja and Ronald Kavanagh, from the biopharmaceutics review team, on 10-21-05. In summary, they indicated that the effect of liver function is operative with oral formulations of selegiline that are absorbed in the gastrointestinal tract due to huge first-pass metabolism. Since EMSAM bypasses this metabolism by virtue of the transdermal absorption of selegiline, selegiline levels from EMSAM are much higher even in subjects with normal liver function and the effect of liver impairment or induction on selegiline levels with EMSAM is thus expected to be insignificant.

With respect to renal impairment, only a very small amount of unchanged selegiline is excreted renally in healthy subjects (less than 1%) and, hence, the effect of renal impairment on selegiline levels is expected to be very minor. In fact, this is consistent with the results of Somerset study 9811, which was described by Dr. Iftexhar Mahmood, the previous biopharmaceutics reviewer, in a review dated 2-28-02. This study examined selegiline pharmacokinetics in three groups of subjects (4 per group) with mild, moderate, and severe renal dysfunction after placement of a single 20mg EMSAM patch for 24 hours. Compared to a historical control group of healthy subjects, the AUC and Cmax of selegiline in subjects with renal impairment were lower by 30% to 45%. AUC and Cmax values were very similar across the three degrees of renal impairment. As Dr. Mahmood noted, it is uncertain whether selegiline levels are truly lower in patients with renal impairment due to the small sample sizes, high variability, and historical control comparisons in this study. Nonetheless, this study does not suggest that renal impairment is associated with markedly higher selegiline exposures as observed in the Anttila study.

C. Potential for Interaction with Oral Contraceptives

A published study by Laine and colleagues suggested a significant effect of oral contraceptives (OC's) on selegiline levels. 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 OC's. The bioavailability of selegiline was drastically increased (20-fold) in those subjects using OC's, with marked increases in both Cmax and AUC.

A second study by Palovaara and coworkers, also in Finland and including Laine as a co-investigator, consisted of a randomized, double-blind, cross-over trial in 12 healthy females who received hormone replacement therapy (HRT) once daily for 10 days containing estradiol and levonorgestrel or matched placebo. On day 10, a single 10mg oral dose of selegiline was taken and selegiline and metabolite levels were assessed for the next 32 hours. The results indicated that, unlike OC's, HRT is not likely to have clinically significant effects on selegiline concentrations.

Somerset provided a response to this issue in an 8-31-05 submission. They present the following arguments against the potential for a significant effect of OC's or HRT on selegiline pharmacokinetics:

- by virtue of transdermal administration, EMSAM avoids a first-pass effect in the liver. Therefore, a reduced first-pass effect is less likely to produce a large increase in selegiline bioavailability compared to oral administration, which was studied in the above investigations.
- EMSAM is metabolized by multiple pathways and inhibition of specific pathways have failed to result in significant pharmacokinetic interactions based on completed interaction studies.
- the studies by Laine and Palovaara produced conflicting data.
- there is no evidence of an interaction based on a Phase 3 population pharmacokinetic analysis. This analysis examined selegiline clearance in depressed females who took 1) no concomitant medication, 2) HRT, and 3) OC's. There was no major difference in median clearance across these groups and there was considerable overlap in the range of clearance values (25-75th percentile and 95% CI's).

As Dr. Kavanagh points out, even when an interaction is known to exist, a population pharmacokinetic analysis may not detect it for a number of reasons. In the case of this analysis, he states that there are insufficient data to evaluate the potential for an interaction. The number of

patients and the number of samples are specified but no other information on this study is provided, to include subject age, when the samples were drawn, or if subjects actually took selegiline and the OC or HRT agent simultaneously. In the end, he felt that no conclusions could be drawn and interaction studies (in vitro and possibly in vivo) with individual hormonal agents would be needed to address this issue.

Strictly speaking, I agree with Dr. Kavanagh that no conclusions can be drawn from this population pharmacokinetic analysis. Although it may be advisable to request these interaction studies as Phase 4 commitments, I am not strongly inclined to do so based on the first two arguments made by Somerset (lack of a first-pass effect with transdermal selegiline and the involvement of several CYP pathways in the metabolism of selegiline). These factors, in my opinion, make it unlikely that a clinically significant drug-drug interaction will occur with the concomitant use of EMSAM and OC's or HRT.

D. Risk for Melanoma

EMSAM Clinical Trials Safety Data

As discussed in my 8-19-05 review, Somerset examined the EMSAM Phase 2/3 clinical trials database to identify any reported cases of melanoma. This database was comprised of 3,365 patients treated with EMSAM, representing 1,123 patient-years of exposure.

The results were submitted on 8-16-05. No cases of melanoma were revealed although, as of that date, three patients from these trials had undergone skin lesion biopsies with unknown results. The sponsor pursued the biopsy results and provided the following information in an Email on 11-2-05:

- Patient 15047 received EMSAM treatment and underwent a biopsy of lesions on her arm and abdomen. The biopsy results indicated that the lesions were benign.
- Patient 02008 received placebo treatment and had a biopsy of a skin lesion, which was found to be benign.
- Patient 0316 received EMSAM treatment and had biopsies of face and hip lesions. The investigational site is no longer active and no further information could be obtained.

Thus, no melanomas were identified in patients from the EMSAM clinical trials.

Eldepryl NDA

The original NDA database for oral selegiline, marketed as Eldepryl, encompassed only about 100 patients because this product was granted orphan drug status.

As we requested in an 8-1-05 teleconference, the sponsor examined safety data from this application. In an Email on 8-24-05, Somerset indicated that no cases of melanoma were identified.

DATATOP Study

The Deprenyl and Tocopherol Antioxidative Therapy of Parkinson's Disease study was initiated under the sponsorship of the National Institute of Neurological Disorders and Stroke (NINDS). In the above-mentioned 8-1-05 teleconference, we requested that Somerset access the safety database from this trial and conduct a search for cases of melanoma among the study patients. The sponsor responded to our request in an 8-31-05 submission.

As background, this trial enrolled 800 subjects with Parkinson's disease between September 1987 and November 1988. The study objective was to obtain a long-term assessment of the impact of selegiline and tocopherol on disability progression in this cohort. Patients were assigned to one of four treatment arms (about 200 patients per arm): placebo, selegiline, vitamin E, or selegiline with vitamin E. Originally, patients were to be terminated when, in the judgement of the investigator, a level of functional disability sufficient to require initiation of levodopa therapy was reached.

Although the study was originally planned to have an observation period of two years, the duration was extended to about eight years to 1) allow for continuation in the trial after initiation of levodopa treatment, 2) permit all patients to receive open-label selegiline, and 3) to provide for a second randomization to either selegiline or placebo in early 1993.

The entire DATATOP safety database was electronically searched by the Parkinson's Study Group to detect any reported cases of melanoma using the search terms "skin malignancy" and "skin incision." All identified cases were

reviewed by a medical monitor. Also, all adverse event pages from all available case report forms were examined to insure that no additional cases of melanoma were reported.

Five cases of melanoma were found. Of these, one occurred on placebo (with no previous selegiline treatment) and four occurred during selegiline treatment, including patients who received levodopa or vitamin E with selegiline. The rates of melanoma per 1,000 patient years of exposure and corresponding 95% confidence intervals were 1.35 (0.50, 3.58) in the selegiline patients and 1.62 (0.23, 11.54) in the placebo patients. Thus, there appears to be no significant difference between selegiline and placebo in the rate of melanoma in the DATATOP trial.

Other Supportive Information

Other supportive information regarding melanoma risk was provided in the sponsor's 8-31-05 submission. This was comprised of a search of the FDA AERS database; analyses from the Ohio Medicaid program, and the U.K. General Practice Research Database (GPRD); and a review of the published literature. None of these sources indicated an association between melanoma and selegiline or MAOI's in general. However, these examinations had significant limitations and, thus, will not be described in detail here.

Summation

Overall, based on the EMSAM clinical trials database, the original Eldepryl NDA safety data, and information from the DATATOP study, there is no current evidence to suggest an elevated risk of melanoma associated with selegiline treatment.

E. — and Impurity Genotoxicity

EMSAM patches were found to contain five impurities felt to be potentially genotoxic:

(((

— is a degradant impurity in the drug substance (and drug product) and the other four entities are — from the adhesive in the patch.

Since these compounds were suspected to be mutagenic, for each it was necessary to either 1) demonstrate lack of mutagenicity or 2) eliminate them or at least reduce their presence to a very minimal amount (i.e., not to exceed—

The sponsor did not conduct further studies as recommended in the approvable letter to ascertain the genotoxicity of these five impurities. Instead, they have provided arguments, primarily based on published literature, to support their contention that these impurities are not a concern. These arguments were examined by Dr. Linda Fossom, the Pharmacology-Toxicology reviewer (see her review dated 11-28-05).

Also, the chemistry reviewer, Dr. Donald Klein, has negotiated with Somerset to lower the specifications for all 5 impurities to the lowest possible level (see his review dated 11-8-05).

Based on the lowered specifications and supporting information, these impurities are not deemed to be of concern by Dr. Fossom. Her conclusions for each impurity are summarized as follows:

- 1) — gave mixed results in the Ames test but was not carcinogenic in oral studies in mice and rats. Based on structure, — is expected to be less reactive than —. Also, amounts of — did not increase over time during stability testing and presumably some low level of — was present in batches used for in vitro genotoxicity assays and oral carcinogenicity studies in animals.
- 2) — the expected daily dose of — with the 40mg dose of EMSAM is —, which is less than twice the accepted limit of —. Also, only — of — appeared to be extracted under conditions simulating moist skin. Finally, although positive for in vitro clastogenicity and arguably positive for in vivo clastogenicity, it was not positive in an inhalation study in rats.
- 3) — in vitro tests for mutagenicity appeared negative. Dermal carcinogenicity studies in mice demonstrated that — could produce local skin tumors in

one study but only at doses that caused local scabbing and scaling for considerable time (over 24 weeks). This effect seems to be related to chronic irritation and not genotoxicity.

4) although positive for in vitro clastogenicity (but negative in the Ames test), it is not considered carcinogenic in an oral study in rats or in a dermal study in mice based on published literature.

5) — the specification for this impurity at the maximum recommended human dose (—), has been lowered to an acceptable level.

One specific clinical recommendation Dr. Fossom advocates is that patients be warned not to apply EMSAM to irritated skin since — appeared to produce skin tumors in mice, probably secondary to severe, prolonged skin irritation (as opposed to a genotoxic mechanism). Current application instructions do inform patients to choose a different application site each day and to not apply the patch to irritated or broken skin.

F. Tyramine Safety

In my 8-19-05 review, I asserted that tyramine dietary restrictions should be implemented for all three EMSAM patch strengths. The sponsor has agreed that restrictions are prudent for the two higher dose patches (30 and 40mg) but contends that the 20mg patch may be safely used without a tyramine-restricted diet. Arguments for and against the sponsor's proposal are presented in that review.

In September 2005, it was decided to take this issue to the Psychopharmacological Drugs Advisory Committee (PDAC). The PDAC met on 10-26-05 and the following two questions were put to the Committee. Formal votes were requested on both.

1) Do the available data for the EMSAM 20mg patch support the reasonable safety of this formulation without the need for dietary restrictions?

With 11 members voting, the outcome was 7 "Yes" and 4 "No." Several members voting in the affirmative appear to have been persuaded by 1) the safe postmarketing experience with Eldepryl, which has been marketed for several years without tyramine restrictions and produces tyramine sensitivity at a typical dose of 5mg bid comparable to EMSAM 20 mg/day, and 2) lack of reports of hypertensive reactions in the

EMSAM Phase 2/3 studies, the vast majority of which did not impose tyramine restrictions and many of which provided no specific information to study participants that would have discouraged the use of tyramine-rich foods and beverages. Two of the votes in the negative were related to concerns about the small numbers of subjects in the tyramine challenge studies.

2) If the EMSAM 20mg patch formulation could be considered reasonably safe for marketing without the need for dietary restrictions, would it be acceptable to market the 20mg patch without dietary restrictions and at the same time require dietary restrictions for the 30 and 40mg patch strengths?

With 10 members voting, the outcome was 6 "Yes" and 4 "No." One particular recommendation was to have the requirement for dietary restrictions printed on each patch as appropriate. The sponsor's presentation to the Committee prior to this vote included a proposed risk management plan that will entail education of patients, pharmacists, and prescribers about the need for dietary precautions at the two higher doses and focused postmarketing surveillance for hypertensive reactions and sequelae. This plan was formally submitted for our review on 11-21-05.

The relatively small amount of data from Phase 1 tyramine studies do suggest a clear effect of EMSAM on MAO-A activity, even with the 20mg patch. But these investigations fail to provide clear evidence of a clinical risk for use of the 20mg patch without tyramine restrictions:

- in study P0045, after administration of the 20mg patch for 30 days, the lowest pressor dose under fasted conditions, seen in one of twelve subjects, was 50mg. Under fed conditions, the adjusted pressor dose in this subject would be 100mg, well above an amount of tyramine that a person would be likely to ingest outside of a experimental setting (estimated maximum of 40mg).
- in the pool of three studies in which the 20mg patch was administered for 9-10 days (P9932, P9940, and P9941), the lowest pressor dose was 200mg (in 19 of 47 subjects) under fasted conditions. Although this is based on only 9-10 days of dosing and tyramine sensitivity does seem to increase over time to about 30 days of treatment, this is

under fasted conditions and is far higher than the amount of tyramine likely to be ingested by a typical patient.

- in study 9802, in which subjects treated with the 20mg patch for 13 days ingested meals containing huge amounts of tyramine (minimum estimated tyramine content of 244mg) followed by close blood pressure monitoring, there was no indication of a tyramine-induced hypertensive reaction.

My stance on this issue, to not approve the 20mg patch without tyramine restrictions, was based for the most part on the large variability in pressor doses, both between subjects and within subjects over time, in Somerset's tyramine challenge studies. Such variability has led me to expect that there will be considerable overlap in tyramine sensitivity between patients using the 20mg patch and patients using the 30mg or 40mg patches. The tyramine safety of the two higher dose patches is considered, at best, unknown at this point in time.

A body of evidence that would permit a rigorous evaluation of this concern does not now exist. A study to produce such evidence would need to randomize a large number of patients to fixed dose treatment at each of the three patch strengths as well as to placebo, a positive control (such as tranylcypromine), and perhaps a negative control drug as well. Such a study would need to enroll a diverse sample of subjects in terms of age, gender, and (to the extent feasible) race; probably should include patients with depression, and should perform multiple tyramine challenges on-treatment to allow for some assessment of the within-subject variability in tyramine sensitivity over time. A study with some of these characteristics was, in fact, recommended by some members of the PDAC.

Alas, such an investigation would be very difficult, if not impractical, to execute. Alternative sources of safety data are the Eldepryl postmarketing safety experience and the EMSAM Phase 2/3 safety data. Each of these has weaknesses relative to a more rigorous study as I described above, for example, lack of systematic, close blood pressure monitoring. On the other hand, these databases also possess several advantages over small tyramine challenge studies in a select group of subjects, to include a large number and variety of patients, lengthy durations of selegiline exposure in many patients, and treatment at all three doses of EMSAM, mostly in the context of no tyramine dietary precautions. As noted by the sponsor

during the PDAC meeting, the informed consent process for about 1,000 of the patients in the EMSAM Phase 3 studies entailed no mention of the possibility of a "cheese reaction," which otherwise might have indirectly discouraged patients in these trials from consuming foods with high tyramine content. It is noted that several members of the PDAC opined that these sources of data provided sound support for the safety of the 20mg patch without dietary restrictions and these opinions appeared to drive the vote outcome in favor of the sponsor's proposal.

It would seem reasonable at first glance to assume that important adverse events resulting from variability in tyramine sensitivity would be realized under the conditions of use prevalent with the postmarketing use of Eldepryl and in the EMSAM clinical trials. But, assuming that tyramine sensitivity varies over time, such events will only occur at times of heightened tyramine sensitivity and ingestion of a high-tyramine foodstuff: both conditions would have to coincide for a hypertensive reaction to occur. This factor reduces the ability to predict vulnerability for a reaction in typical clinical usage compared to a tyramine challenge study, where at least the tyramine intake is controlled. Nonetheless, given the large exposures to selegiline with the postmarketing use of Eldepryl and the clinical trials experience with EMSAM, at least a small number of reactions might be expected.

But there is very scant evidence of such reactions. Based on the sponsor's examination of safety data from these sources, there was one possible hypertensive crisis from the Eldepryl postmarketing experience and no cases from the EMSAM clinical trials.

My own survey of the selegiline postmarketing experience consisted of a search of the FDA AERS DataMart for adverse reactions coded as "hypertensive crisis" where any selegiline product was the suspect drug. There were no time limits imposed on this search. This process yielded only one hypertensive crisis (ISR #3838619), which had been published by Ito and coworkers.⁶ My examination of this report suggests that this reaction was not due to tyramine ingestion and may not have been related to selegiline since this reaction recurred over a few week period after stopping drug. Given the narrowness of my search criteria

⁶ Ito D, et al. Paroxysmal hypertensive crises induced by selegiline in a patient with Parkinson's disease. J Neurol 2001;248:533-534.

and underreporting that is common in postmarketing surveillance, this result likely underestimates the true incidence of hypertensive reactions associated with selegiline. Nonetheless, it does not appear that tyramine-related hypertension has been a major safety problem with Eldepryl. Likewise, I am not aware of any clearly documented cases of tyramine-related hypertensive events in the EMSAM Phase 2/3 studies.

Another concern broached in my last review was the possibility of significantly elevated selegiline levels (and, *pari passu*, elevated tyramine sensitivity) in certain patient populations, such as in elderly females, patients with hepatic or renal impairment, or females using oral contraceptives. These specific issues have been addressed by the biopharmaceutics review team (see above). I do not expect that these specific factors will produce significant elevations in selegiline levels although further study in old and very old patients should be considered, as advocated by Dr. Kavanagh in his review and in our 1-30-04 approvable letter.

In the end, despite the lack of an ideal body of evidence pertaining to the tyramine safety of EMSAM, I am now satisfied that there is adequate evidence to support the approval of the EMSAM 20mg patch without tyramine restrictions.

The PDAC vote on the second question indicates that most Committee members felt reasonably comfortable with requiring dietary restrictions at the two higher doses with none at the lowest dose. Somerset's risk management plan is intended to reduce confusion and help insure the appropriate use of EMSAM vis-à-vis dietary tyramine intake (see below). Although 100% compliance and safety can never be assured, I do think that with a solid risk management plan, EMSAM 20mg can be safely used in the clinical setting without tyramine restrictions.

G. Risk Management Plan

Chad VanDenBerg, Pharm.D., of Somerset Pharmaceuticals, presented an outline of a proposed Provider/Patient Awareness plan to the PDAC. The goal of this plan is to assure 100% awareness of the need for dietary modifications with the higher dose patches of EMSAM (30 and 40mg).

Based on this outline, the primary elements are 1) educational and outreach tools for prescribers, pharmacists, and patients and 2) uniquely designed packaging, with the statement "Dietary Modifications Required" in red letters on the front of the boxes of the EMSAM 30 and 40mg patches. Additionally, there will be a pharmacovigilance program that will include education on event reporting procedures along with targeted follow-up on specific adverse events, such as hypertensive crisis and other cardiovascular events.

A study of physician and patient comprehension of the need for dietary modifications was performed using 75 physicians (i.e., psychiatrists and primary care doctors) and 70 patients. After one "exposure," 96% of physicians and 94% of patients correctly identified the need for dietary modification at higher doses.

The details of this plan were formally submitted for Agency review on 11-21-05. This plan will be forwarded to the Office of Drug Safety as a consultation request for review.

H. Potential QT Prolongation

A possible signal for prolongation of the QT interval on ECG was found with a closely related product, Zelapar or zydis selegiline, an orally disintegrating formulation of selegiline. This product was developed as an adjunct in the treatment of patients with Parkinson's disease and an application for Zelapar was submitted to the Division of Neurology Products (DNP) by another sponsor as NDA 21-479.⁷

This finding derived from a closely monitored ECG study that examined two fixed doses of Zelapar (2.5 and 10 mg/day) as well as placebo and moxifloxacin comparison arms. It is notable that the traditional analyses of ECG data for this product (mean change from baseline in ECG parameters and the proportion of patients with outlier values) did not suggest QT prolongation. Rather the above finding was based on a recently developed criterion for detecting potential QT prolongation (i.e., a value of 10 msec or greater for the upper bound of the 95% confidence

⁷ See the clinical review by Dr. Leonard Kapcala dated 9-29-05 for details.

interval for the largest time-matched difference between drug and placebo).⁸

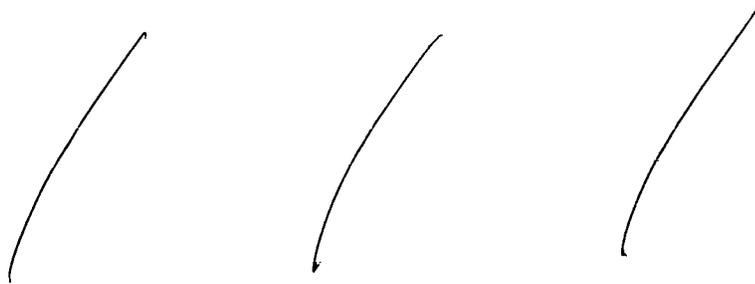
After discussion of this study at the Team Leader and Division Director levels within DNP, it was concluded that the data did not show clear evidence of QT prolongation associated with Zelapar and no further evaluation of the effect of Zelapar on the QT interval was deemed necessary.⁹

Based on my examination of data from this investigation, I likewise do not feel that there is convincing evidence to suggest a QT prolongation effect with Zelapar. Given this and the lack of a signal for QT prolongation from the EMSAM clinical trials using our commonly used methodology, I see no need for further examination of the effects of EMSAM on the QT interval at this time.

I. Labeling Revisions

Somerset submitted their proposal for EMSAM product labeling, including a Medication Guide and Patient Information Leaflet, in the 5-26-05 response to our approvable letter. Comments on those documents from a clinical perspective are offered in my 8-19-05 review.

On 11-3-05, Somerset submitted revisions to their previous proposal. Changes are intended to address comments from my last review as well as deliberations of the PDAC. Clinical comments on these revisions are as follows. (I have not specifically commented on those revisions which appear to be acceptable.)



⁸ See ICH Guideline E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

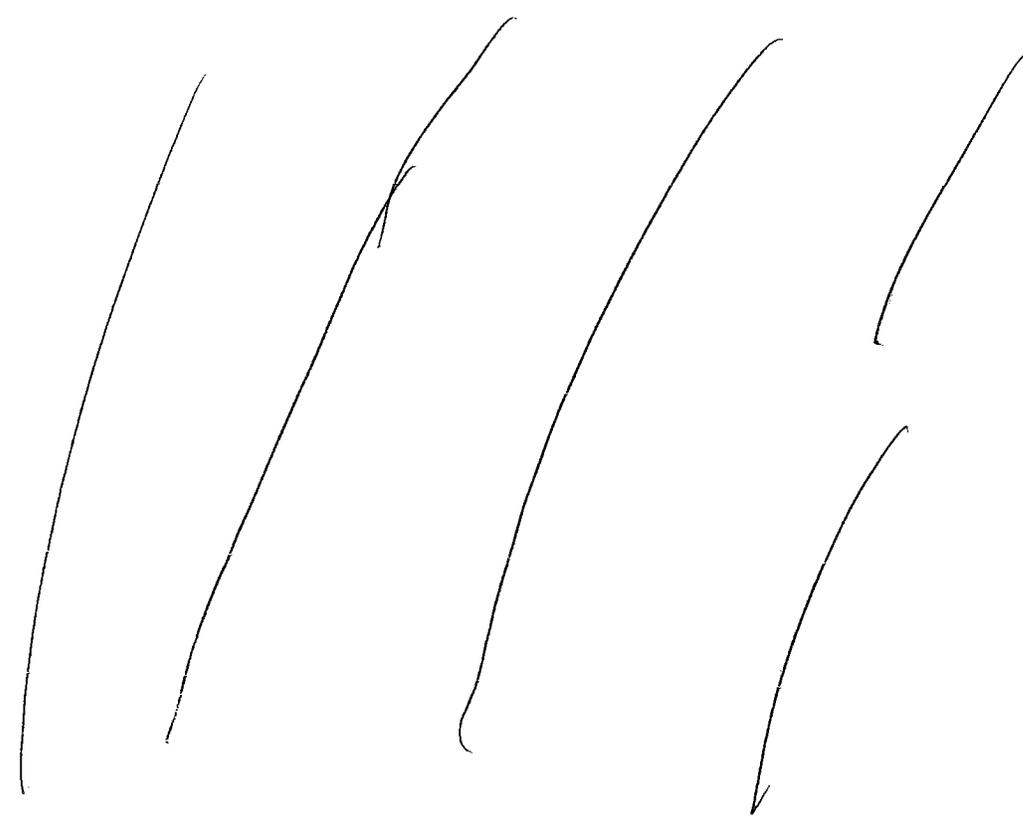
⁹ See memoranda filed under NDA 21-479 by Dr. John Feeney (9-30-05) and Dr. Russell Katz (9-29-05).

2 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process



III. Recommendations

From a clinical perspective, I continue to view this application as approvable until the following three issues are addressed:

- 1) final labeling. The outstanding clinical issues for labeling raised in section II.I above should be addressed by the sponsor.
- 2) risk management plan. The details of this plan should be reviewed by the FDA Office of Drug Safety. Any recommended modifications to this plan will need to be negotiated with Somerset.
- 3) Our 1-30-04 approvable letter requested an assessment of the performance of the EMSAM patch in the elderly (age 65 years and older). According to the biopharmaceutics review team, this request has not been adequately addressed to date. It seems reasonable to address this issue as a Phase 4 Commitment. However, it is recommended that we reach

agreement with the sponsor on more specific requirements for satisfying this request prior to approval.

Finally, it is noted that a meeting was held with the Office of Drug Safety on 10-31-05 to convey our recommendation that, if and when EMSAM is approved, postmarketing surveillance include a focus on reports of the following events: hypertensive reactions and their sequelae, systemic allergic reactions, psychotic symptoms, melanoma, and non-melanoma skin cancers.

Gregory M. Dubitsky, M.D.
November 29, 2005

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

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Greg Dubitsky
11/29/2005 01:08:52 PM
MEDICAL OFFICER

Paul Andreason
1/22/2006 04:47:43 PM
MEDICAL OFFICER

Dr Dubitsky now believes that tyramine dietary restrictions are not necessary for the 20-mg/day dose. I agree that tyramine dietary restrictions are not necessary for the 20-mg/day transdermal dose.

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 which delineated the following clinical matters to be addressed prior to final approval:

- regulatory update and foreign labeling.
- safety update and world literature update.
- labeling.

In addition, this letter listed a number of requests from other disciplines:

- recommendations from the Division of Medication Errors and Technical Support (DMETS) regarding the patch label, pouch label, and carton labeling. Also, we advised Somerset that the proprietary name for STS, EMSAM, will need to be reassessed by DMETS about 3 months prior to the expected approval of this application.
- requests from the Nonclinical Pharmacology and Toxicology reviewer, including the need for a 2 year carcinogenicity study in the mouse using the dermal route.
- CMC requests for a _____ and demonstration of potentially mutagenic compounds at concentrations not to exceed _____
- requests from the Clinical Pharmacology and Biopharmaceutics reviewer, including studies of adhesion, dermal tolerability, and STS performance in the elderly.
- copies of introductory promotional materials to be sent to the Division of Drug Marketing, Advertising and Communications.

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.

Subsequent to this submission, the Division also determined that a systematic evaluation of selegiline clinical trial data for the emergence of melanoma was needed due to a signal for this malignancy with another MAOI compound. A request for this information was forwarded to Somerset in a letter dated 6-15-05. On 7-21-05, Somerset responded to this request. This submission is also reviewed below.

II. Review of Clinical Issues

A. Regulatory Update and Foreign Labeling

B. Safety Update and World Literature Update

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 ($N_{STS}= 817$, $N_{\text{placebo}}= 668$).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.

2. Worldwide Literature Update

a. Search Methodology

The sponsor searched the published clinical literature on selegiline from September 2003, which was the cut-off date of their most recently submitted literature search, to March 2005.⁷ This search was not limited to the transdermal route of administration but encompassed all routes of administration and all age groups. The search was conducted by _____ using Medline, Embase, and Biosis Previews.

Identified references were reviewed by Albert Azzaro, Ph.D. (pharmacology), who is the Chief Scientific Officer for Somerset. Dr. Azzaro handpicked references according to relevance. Papers were excluded if selegiline was used only as an investigational tool, selegiline was not the focus of the study, or if the paper reviewed only previously published data. Abstracts were excluded unless they were deemed to be of special relevance.

The sponsor summarized selected articles in an Executive Summary. The clinical section of this summary is reviewed below.

b. Search Results

With two exceptions, the sponsor states that no unexpected side effects or previously unknown toxicities of selegiline were revealed in the literature search.

The first exception is a French article assessing the risk-benefit ratio of a sublingual selegiline formulation.⁸ It

⁷ The search also included non-clinical data, which will be reviewed by the FDA Pharmacology/Toxicology reviewer in a separate document.

⁸ [No author listed.] Sublingual selegiline. New Formulation: New Risk of Oral Adverse Effects. *Prescrire International*. 2003;12(67):179.

reports that this formulation is not acceptable for the treatment of patients with Parkinsonism since it failed to show a decrease in amphetamine-related adverse effects and was associated with five cases of mouth ulceration and stomatitis.

Comment: There may be a difference in local sensitivity between mucosal contact and absorption of the sublingual tablets versus transdermal contact and absorption of selegiline via the STS patch. Thus, the implications of mouth ulceration and stomatitis with the sublingual tablets for STS are not clear. In any case, application site reactions have been commonly observed in clinical trials with STS treatment but skin ulceration apparently has not been reported.

The second exception is a published open-label study from Finland.⁹ This investigation compared the pharmacokinetics of oral selegiline among four parallel subject groups: 1) patients with liver disease, 2) patients receiving a drug that induces hepatic enzyme activity, 3) patients with impaired kidney function, and 4) control subjects. There were 10 subjects in each group. A single 20mg tablet of selegiline (Eldepryl) was administered after an overnight fast. Blood specimens were collected over the next 48 hours and analyzed for concentrations of serum selegiline and its main metabolites.

Compared to normals, the AUC for selegiline was, on average, 18-fold higher in patients with impaired liver function ($p < 0.05$), 23-fold lower in patients with drug-induced liver function ($p < 0.001$), and 6-fold higher in patients with impaired kidney function ($p < 0.05$). There was large variation among individuals within each group. The authors conclude that these results suggest the need for dosage adjustment when selegiline is used in patients with altered liver or kidney function.

Comment: The results of previous studies conducted by Somerset in patients with hepatic and renal impairment using STS are not consistent with those in this published investigation.¹⁰ This published study will be further

⁹ Anttila M, et al. Marked effect of liver and kidney function on the pharmacokinetics of selegiline. Clin Pharmacol Ther 2005;77:54-62.

¹⁰ See the biopharmaceutics review by Dr. Iftexhar Mahmood dated 2-28-02 as well as proposed labeling for EMSAM conveyed with the 1-30-04 approvable letter.

evaluated by the current biopharmaceutics reviewer to determine if current dosing recommendations in these patient populations should be modified.

My examination of the clinical literature summary revealed no other findings that could impact on the approvability of this application or warrant a labeling change.

C. Potential Melanoma Risk

On 7-21-05, Somerset responded to our request for a review of available selegiline databases for cases of malignant melanoma. This request applied to both oral formulations of selegiline (Eldepryl tablets and capsules) as well as the selegiline transdermal system (EMSAM).

Regarding the EMSAM safety database, their search of Phase 2/3 clinical databases for the selegiline transdermal system consisted of a two-tiered review process:

- Level-1 involved an electronic search of all EMSAM studies for the following COSTART preferred terms: carcinoma, carcinoma skin, melanoma skin, neoplasm skin, granuloma skin, hypertrophy skin, skin disorder, and skin discoloration.¹¹ The generated listings were examined by the physician monitor who was blinded to treatment. Cases which met any of the following criteria were selected for review at the next level:

- all carcinoma without a primary source.
- all melanoma.
- all skin carcinoma.
- all moles.
- unexplained skin discoloration.
- undefined hyperkeratosis or skin lesions:
- any skin lesion biopsied or removed with cryosurgery.

- Level-2 entailed a review of case report forms for the selected adverse events by the medical monitor to detect any cases of melanoma.

¹¹ Complete adverse event listings for three studies (E100-94B, E102-96B, and E110-97B) were reviewed by the medical monitor due to inability to access computerized databases for these trials.

The EMSAM Phase 2/3 database consists of 3,365 unique STS-treated patients to date.¹² This represents 409,920 patient-days (or 1,123 patient-years) of exposure. A total of 695 patients have been exposed only to placebo in Phase 2/3 trials.

The Level-1 review identified 114 adverse events. Of these, 50 events in 46 patients were selected for Level-2 review (38 events from STS-treated patients and 12 from placebo-treated patients).

No cases of melanoma were revealed.

Ten STS-treated patients experienced non-melanoma skin cancers (13 adverse events). Eleven were cases of basal cell carcinoma and two were cases of squamous cell carcinoma. Among these ten patients, four had a prior history of skin cancer and a fifth patient had squamous cell carcinoma at screening. Thus, in the total Phase 2/3 database, the crude incidence of non-melanoma skin cancer in STS patients was 0.3% (10/3,365) or 0.9 per 100 patient-years.

The largest number of skin cancers came from study E101-96B, a 48 week placebo-controlled trial of STS 20mg/20cm² in 406 patients with Alzheimer's disease (ages 51-85 years). Based on a previous review of safety data from this trial, there were 11 occurrences of non-melanoma carcinoma, 9 among 7 STS patients (N=273) and 2 in placebo patients (N=133).¹³ The crude incidence of skin carcinoma was greater in the STS group but this difference was not statistically significant (2.6% vs. 1.5%; p=0.72). Exposure-adjusted rates (per 100 patient-years) were 4.0 for STS and 2.2 for placebo. The breakdown by type of carcinoma is as follows:

<u>STS</u>	<u>PLACEBO</u>
Basal Cell Ca (7)	Basal cell Ca (1)
Bowen disease (1)	Other (1)
Squamous cell (1)	

¹² Note that the 7-21-05 submission contains an erroneous number of STS-treated patients (2,467). In a telephone conference on 8-15-05, the sponsor indicated that the correct figure is 3,365. The patient-days of exposure (409,920) is correct as submitted.

¹³ See the Review and Evaluation of Clinical Data dated 3-14-02 (page 28).

Of the 7 STS patients with skin cancers in this trial, 6 had cancerous growths on the face or head, making it unlikely that they occurred in the area of STS patch placement.

From the entire EMSAM Phase 2/3 database, a total of 28 skin lesions were biopsied or treated with cryosurgery. The results from 25 of these are known and reveal no evidence of melanoma. Information on the remaining three cases is being pursued by Somerset and will be submitted when available.

Somerset stated that databases for Eldepryl tablets and capsules which would permit a search for cases of melanoma do not exist since the tablets were approved under orphan drug status in 1989 and the capsules were approved based on bioequivalence data.

A teleconference was held with the sponsor on 8-1-05 to discuss our 6-15-05 request for melanoma information. Somerset stated that the original NDA for Eldepryl as an orphan drug is about 20 years old and encompassed data from only about 100 patients. Files are not in electronic format but they did agree to extract the requested data and submit it in the requested format. We also requested that they seek access to data from the DATATOP study and, if possible, submit it in similar fashion.¹⁴ Information from these non-EMSAM databases is pending at this time.

Comment: Based on a lack of cases in the Phase 2/3 database (N=3,365), one would not expect the true incidence of melanoma in EMSAM-treated patients to be greater than 1/1,122 or 0.09%. This must be taken with a grain of salt, however, since these studies did not, to my knowledge, utilize systematic dermatologic examinations to identify skin lesions. Thus, it is possible that some cases of melanoma were undetected. Also, as noted above, biopsy results from three cases are still pending from the sponsor.

¹⁴ DATATOP, or the Deprenyl and Tocopherol Antioxidative Therapy of Parkinson's Disease study, enrolled 800 subjects between September 1987 and November 1988. The objective was to obtain a long-term (several year) assessment of the impact of selegiline and tocopherol on disability progression in this cohort. (See Marras C, et al. Survival in Parkinson disease: Thirteen-year follow-up of the DATATOP cohort. *Neurology* 2005;64:87-93.)

Regarding the excess number of non-melanoma skin cancers in STS-treated patients versus placebo patients in study E101-96B, this finding is unexplained but could be due to chance. Perhaps data from the oral selegiline database or the DATATOP study will shed further light on this issue.

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
Tranlylcypromine (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, tranlylcypromine.

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.

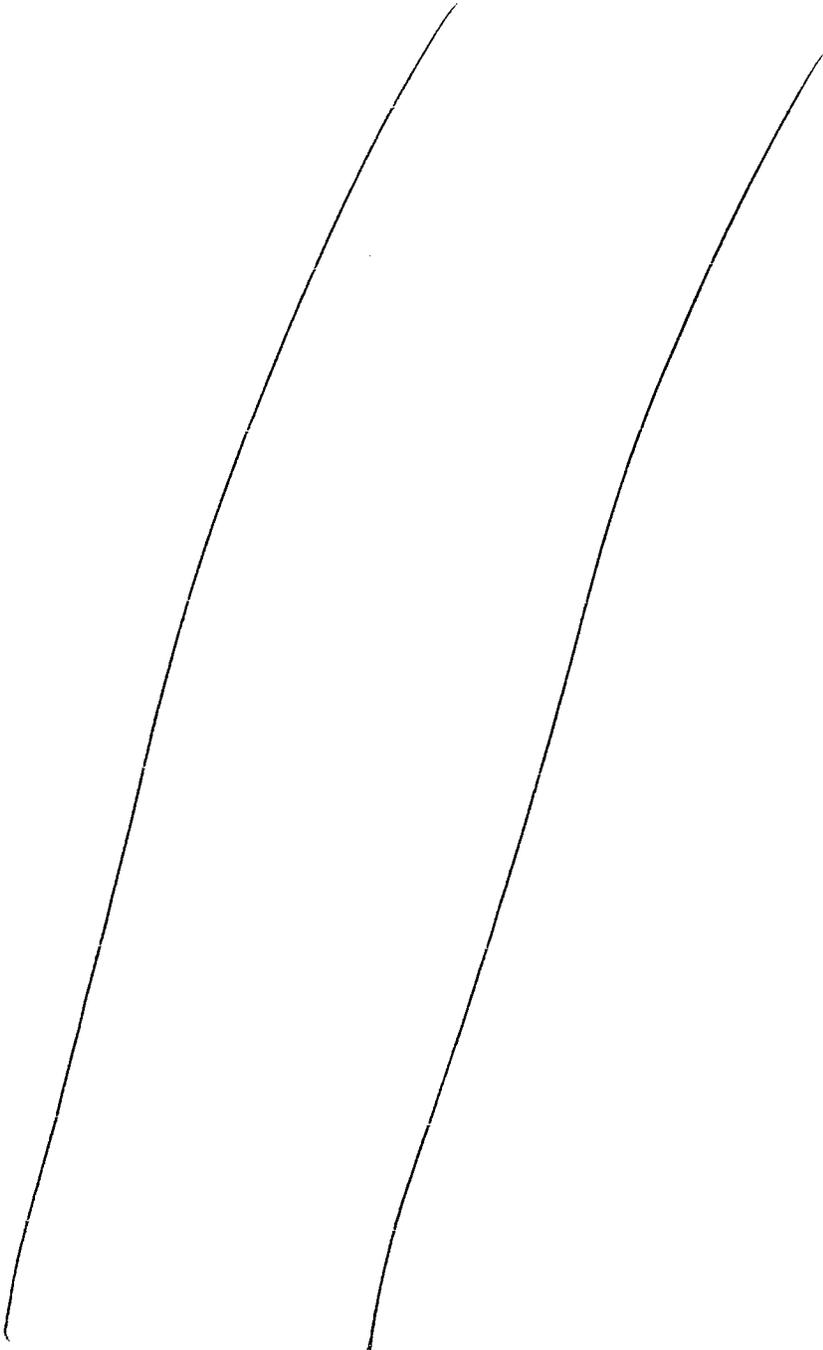
Another possible specific source of variability is an interaction with agents that elevate selegiline levels. One particular concern is a possible effect of oral contraceptives on selegiline levels, as reported by Laine and colleagues.²¹ This Finnish study compared selegiline and desmethylselegiline 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

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.

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.

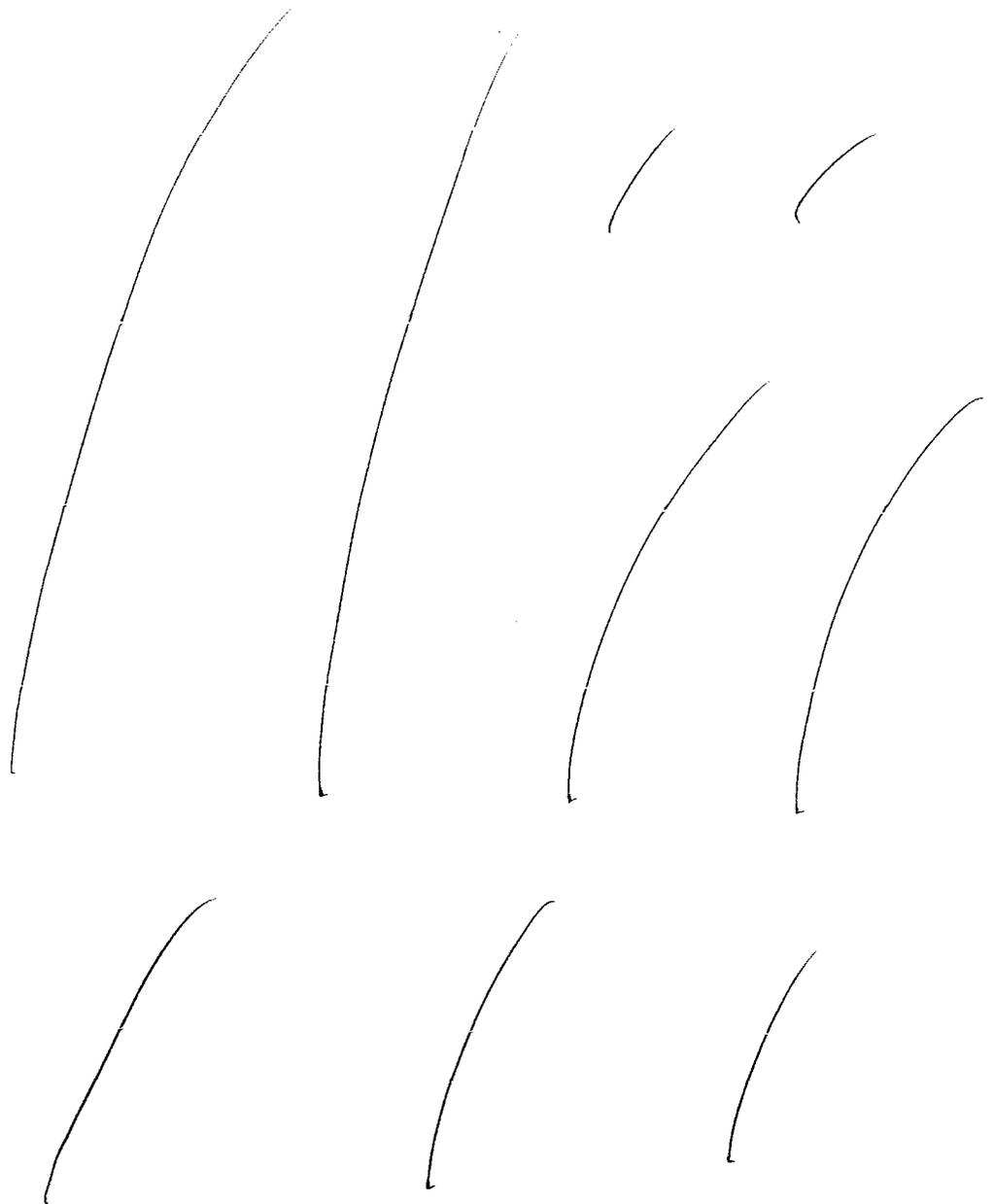


4 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process



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.

1) determination _____ in elderly patients, particularly older females, based in part on a population pharmacokinetic analysis submitted by the sponsor.

2) determination _____ patients with altered liver or kidney function, based in part on a published study identified in the sponsor's literature search (Anttila and coworkers).

3) determination _____ in females using oral contraceptives, based in part on a published study (Laine and coworkers).

The above three issues are to be addressed by the biopharmaceutics staff.

4) an assessment of the risk for melanoma with oral selegiline based on data from the original Eldepryl NDA safety database and from the DATATOP study. This assessment is being led by the Neurology Division Safety Team.

5) Somerset follow-up on the skin biopsy results for three patients identified in their search for occurrences of melanoma in the EMSAM safety database.

6) assessment of the genotoxicity of four _____ in the EMSAM adhesive patch and, as appropriate, specification of limits for these entities in the patch.²⁴ This issue is being addressed by both the chemistry and pharmacology/toxicology staffs.

7) negotiation of labeling with Somerset (see my above labeling review and recommendations).

The above issues will be addressed in an addendum to this review after other reviews have been completed.

In addition, it is recommended that the Office of Drug Safety be advised that the following adverse events deserve particular attention in their surveillance of postmarketing safety reports after EMSAM is approved:

²⁴ See the 7-15-05 Email from Amit Mitra to Donald Klein, the chemistry reviewer.

- hypertensive reactions, to include possible sequelae such as subarachnoid hemorrhage and heart failure.
- allergic reactions and psychotic symptoms. Multiple reports of these events were identified in this review of premarketing data. Although I am not sufficiently convinced at this time that these events are causally linked to EMSAM and merit prominent labeling, they may. Postmarketing safety data may shed more light on these concerns.
- skin cancers. This should include both melanomas, which were observed with a related compound, and non-melanomas, which were seen at a non-significantly higher rate with STS than with placebo in a long-term study of EMSAM in patients with Alzheimer's disease (see above).

I recommend that this application be deemed approvable until the above issues are satisfactorily resolved.

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	Anorgasmia
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

**This is a representation of an electronic record that was signed electronically and
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

MEMORANDUM

DATE: January 29, 2004

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-336

SUBJECT: Action Memo for NDA 21-336, for the use of Emsam (selegiline transdermal system) Patches in the treatment of patients with Major Depressive Disorder (MDD)

NDA 21-336, for the use of Emsam (selegiline transdermal system) Patches in the treatment of patients with Major Depressive Disorder (MDD), was submitted by Somerset Pharmaceuticals, Inc., on 5/24/01. Selegiline is currently marketed by Somerset as Eldepryl, an oral dosage form approved for the treatment of patients with Parkinson's Disease at 5 mg BID. The division issued a Not Approvable letter to the sponsor on 3/25/02; the reason for the Not Approvable action was that the division had concluded that the sponsor had not provided evidence of effectiveness from more than one adequate and well-controlled study (a total of four controlled trials had been performed and submitted).

Numerous other deficiencies were noted in the letter as well, although they were not the basis for the Not Approvable action. These deficiencies included problems related to the coding of adverse events, as well as requests for further evaluation of several adverse events, including 1) the potential for the treatment to be associated with the so-called "cheese" (tyramine) reaction, 2) the potential for interactions with TCAs, MAOIs, and SSRIs, 3) postural hypotension, 4) thyroid function, and 5) sexual dysfunction. Additional requests included requests for the submission of electronic data for the animal carcinogenicity data, a repeat Ames test, clarification of the adequacy of the in vivo cytogenetics assay, and numerous CMC questions.

The sponsor responded to the Not Approvable letter in a submission dated 7/31/03. The submission contained the results of an additional short-term study as well as a randomized withdrawal maintenance study. It further contained the requested pharmacology/toxicology and CMC data. This response has been reviewed by Dr. Don Klein, chemist (review dated 1/29/04), Dr. Paul Roney, pharmacologist, Roswitha Kelly, carcinogenicity statistician, Dr. Lois Freed, pharmacology team leader (memo dated 1/30/04), Dr. Ron Kavanagh, Office of Clinical Pharmacology and Biopharmaceutics (review dated 1/14/04), Dr. Greg Dubitsky, medical officer (review dated 12/16/03), Dr. Tristan Massie, statistician (review dated 12/22/03), and Dr. Tom Laughren, psychiatric drugs team leader (memo dated 1/16/04). The review team recommends that the application be considered approvable.

As noted above, the sponsor has submitted the results of two controlled trials, a short term, acute treatment trial (in which a flexible dose range of 20-40 mg was administered and compared to placebo), and a randomized withdrawal study. In this latter study, in the open-label run-in portion, patients met responder criteria for an average of about 25 days. As the review team notes, both studies yielded statistically significant between treatment differences favoring transdermal selegiline.

The sponsor performed an adequate re-coding of adverse events, and review of the re-coded data revealed no adverse event that would preclude approval. Postural hypotension was seen to be dose related (and more prominent in elderly patients). A very slightly increased incidence of elevated total T4 on drug compared to placebo was noted (3% vs 0.8%, respectively), presumably related to an increase in protein-bound hormone (there were no important differences in the incidence of elevated free T4). Application site reactions (ASR) represented the adverse event with the largest attributable risk (in the controlled trials, 24% of drug treated patients developed an ASR compared to 12% of placebo patients).

In the original submission, the review team had noted that there was a decrease in the tyramine dose resulting in a hypertensive response over time (out to about 30 days). In the Not Approvable letter, we had asked the sponsor to further evaluate this potential signal by examining whether this trend continued beyond 30 days. The re-submission contains the results of a longer term tyramine challenge study (patients were treated for about 90 days with EMSAM 40 mg and their response to tyramine was assessed at baseline and after 30, 60, and 90 days of EMSAM treatment; unfortunately, the study was not a randomized, placebo controlled trial, making interpretation of the results difficult). The study, though, appeared to confirm the initial finding, and documented no further decrease in the tyramine dose resulting in a hypertensive response beyond 30 days. As Dr. Dubitsky notes, the mean pressor dose of tyramine decreased from 575 mg at baseline to 84 mg at the end of the study at 30 days and 88 mg at 90 days. Further, between 45-60% of patients had tyramine pressor doses of less than or equal to 50 mg at days 30-90 (see Dr. Dubitsky's Table VII-6, page 53). As he notes, a typical tyramine rich meal contains about 40 mg of tyramine.

The sponsor argues that no cases of hypertensive crises have emerged from the experience with over 2000 patients,

However, I am inclined to agree with Dr. Dubitsky that the fact that these patients were not monitored closely for change in blood pressure, combined with the fact that we have no information about the tyramine content of their meals, and the fact that there is not a very large experience at the 40 mg patch dose, makes this "benign" experience largely uninterpretable, vis-à-vis the capacity of EMSAM to induce the cheese reaction. For this reason, despite the design flaws of the study, I agree with the review team that we should include language in labeling that warns about the necessity for dietary restrictions.

There are several other issues that need to be addressed.

The chemists request that the sponsor develop a _____ to determine the _____ of the product. More importantly, they have determined that five identified impurities are potentially mutagenic. We will ask the sponsor to lower the limit of each of these to less than _____, if they cannot be eliminated completely. If the sponsor cannot lower the limit of each impurity to less than _____ they will need to perform genotoxicity testing of these impurities to directly determine their genotoxic potential.

Finally, problems remain with the sponsor's pre-clinical data.

Drs. Roney and Freed have concluded that the mouse carcinogenicity study is inadequate (both the mouse and rat carcinogenicity studies were performed with oral selegiline). Specifically, the study was only 78 weeks in duration (instead of the typical 102 weeks), not all organs were examined histopathologically, and the data at the high dose were inadequate because of significant weight loss at this dose (marked weight loss is considered to reduce the sensitivity of the assay to detect tumor formation). There were no significant tumor findings at any dose in this study. The sponsor has provided no kinetic data for selegiline or its metabolites in this study.

In addition, the lack of complete organ histopathology and weight loss in the high dose group were also problems in the rat carcinogenicity study. As Dr. Freed notes, however, a 6 month rat study did provide complete organ histopathology, and no tumors were noted. Also, as Dr. Freed notes, plasma levels of the three main metabolites in the mid-dose group in the rat carcinogenicity study were similar to those in humans at the 40 mg dose, although levels of the parent in the rat study were considerably lower than those in humans at the 40 mg dose (the study was clearly an MTD study, however). The Executive CAC, in a meeting on 1/8/02, also concluded that the mouse study was inadequate, and an adequate study should be conducted.

As both reviewers note, the sponsor has not evaluated the carcinogenicity, or the chronic local toxicity, of transdermal selegiline. For this reason, Dr. Freed recommends that the sponsor perform, in Phase 4, a 2 year transdermal carcinogenicity study in the mouse. This study would not only assess the systemic and local carcinogenic potential of the drug when given transdermally, but such a study may be able to produce higher systemic levels of selegiline than were achieved in the oral carcinogenicity studies.

There has been considerable discussion over the last several years with the sponsor about the adequacy of the carcinogenicity assessment of this product. The record of these discussions is somewhat unclear, but it appears that the division had, at some point, informed the sponsor that the studies were

adequate. (Although there is a suggestion that this endorsement only referred to the issue of whether or not adequate exposure to the relevant circulating moieties had been established, and not to the other aspects of the study [e.g., too few organs examined, study duration too short], the record is also not entirely clear on this point. Further, even this "endorsement" appears to have been predicated on the sponsor's original claim that 20 mg was the effective dose; their second controlled trial employed doses as high as 40 mg.) In any event, although the exposure to the parent compound in these studies was undoubtedly considerably lower than that seen in humans at the effective doses, the combined exposure to all four circulating species (parent and the three main metabolites) is somewhat comparable between animals and humans. Further, the rat study, while also not ideal, can be interpreted (there are no significant findings), and the mouse study, while clearly not entirely adequate, does provide some useful data. For these reasons, then, we will not require additional carcinogenicity studies prior to approval. However, I do agree with Drs. Roney and Freed that the mouse study should be repeated, and, as Dr. Freed recommends, it should be done with transdermal administration of drug.

In addition, Dr. Freed notes that the in vivo mouse micronucleus assay was done with oral selegiline. Given that we do not have kinetic data in the mouse, we cannot be certain that appropriate levels of selegiline have been tested in this assay. We will ask the sponsor to justify the use of oral dosing in this model; if they cannot, they will need to repeat the assay in which appropriate exposures are achieved.

For the reasons given above, then, I will issue the attached Approvable letter, with the appended draft labeling.

Russell Katz, M.D.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Russell Katz
1/30/04 03:42:01 PM
MEDICAL OFFICER

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: January 16, 2004

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Emsam (selegiline transdermal system [STS])

TO: File NDAs 21-336 and 21-708
[**Note:** This overview should be filed with the 7-31-03 response to our 3-25-02 nonapprovable letter.]

1.0 BACKGROUND

Selegiline transdermal system [STS] is a patch formulation of selegiline, a monoamine oxidase inhibitor (MAOI) that is currently marketed as Eldepryl (an immediate release capsule for oral administration) as an adjunctive treatment for Parkinson's disease. It is being proposed for the treatment of depression, at a dose of 20 mg (a 20 mg/20 cm² patch delivers approximately 6 mg of selegiline over a 24 hour period). MAO exists as two isoenzymes, A and B, and these isoenzymes have a role in the catabolism of neurotransmitter amines such as NE, DA, and 5HT. At low concentrations, selegiline is selective for MAO B, but at higher concentrations, it inhibits both A and B. In fact, inhibition of both isoenzymes may be necessary for the antidepressant action of STS, since it was positive in the forced swim test (an animal model for depression) only at doses that inhibited both isoenzymes. Since MAO in the gut wall is also important in the catabolism of certain dietary amines (e.g., tyramine), one concern about MAOIs is their potential to inhibit gut MAO-A, resulting in the "cheese reaction." However, the STS formulation avoids exposure of gut wall MAO-A to selegiline, and "cheese reactions" have not been observed with STS, even without the dietary restrictions that need to be observed with orally administered, nonselective MAOIs. Thus, STS might be expected to have the advantage over other MAOI's marketed in the US for depression (phenelzine, tranylcypromine, and isocarboxizide) of not being associated with the "cheese reaction."

The original NDA for STS was submitted 5-24-01, and we issued a nonapprovable letter on 3-25-02 (**Note:** See my 3-15-02 memo to the file for a more detailed discussion regarding this original submission and our nonapprovable action). The deficiency that was the basis for the NA action was a failure to provide sufficient evidence of effectiveness. The NDA had included efficacy data for 4

short-term trials, and we were in agreement on the interpretation for 3 of these trials. In particular, we agreed that study S9303-E106-96B was a positive trial, and that studies S9303-E113-98B and S9303-E114-98B were negative trials. We were not in agreement about the interpretation of study S9303-P9804. We did not consider this a positive study, based on the protocol specified analysis. Since, in all 4 studies, the highest dose or the only dose was 20 mg, we recommended in our NA letter that the sponsor explore dose response for effectiveness in future studies.

In addition to this critical deficiency regarding effectiveness data, we noted in the letter the following deficiencies that should be addressed in a response to our letter:

-Safety Issues:

-Problems in Coding of Adverse Events: We noted serious problems in their methods of coding adverse event data, and asked that they completely redo the coding and then also recreate the adverse event tables.

-Potential for "Cheese Reaction": We asked the sponsor to repeat the tyramine challenge studies for up to 60 days of STS use, and at the highest STS doses that are being proposed for use, given the finding of decreasing tyramine pressor doses over time in studies carried out to 33 days. We also asked for the full report for the PPA interaction study.

-Potential for Interaction with TCAs, MAOIs, and SSRIs: We asked for _____

-Adverse Events Related to Postural Hypotension in the Controlled Depression Trials: Once they have recoded the verbatim adverse event terms (see above), we asked them to review the frequency of AEs potentially related to postural hypotension, since there was a signal for STS-related orthostasis based on analyses of vital signs data.

-Thyroid Function: We asked them to measure free T4 levels in future STS trials, given the finding of elevated total T4 levels in earlier trials.

_____ In their original submission, the sponsor sought _____
/ / / / / / / /

-Nonclinical Pharmacology and Toxicology Issues:

-We noted the continuing need for complete data sets for the rat and mouse carcinogenicity studies.

-We noted the need to repeat the Ames test.

-We asked for additional assurance that the in vivo cytogenetics assay was adequately conducted.

-CMC Issues:

-We conveyed several CMC deficiencies.

-Biopharmaceutics Issues: There were none; we simply noted our acceptance of their proposed dissolution specifications.

-Pediatric Rule: We indicated that any requirements for pediatric studies under the final rule would be deferred until the issues for approvability of the adult claim could be resolved.

Following the 3-25-02 nonapprovable letter, we held a 4-2-02 telcon with the sponsor, and then a 5-2-02 face-to-face meeting. We reached agreement on the following:

-New efficacy study and support for safety of higher dose range utilized: They had initially argued that their completed randomized withdrawal study (P9806) should count as a second positive study, however, we disagreed, arguing that this study answers a different question. The sponsor then asked if study 52 would suffice as a second study. This is a flexible dose study (20-40 mg/day). We said yes, but relying on this study would then raise the question of adequacy of safety data at the higher dose range that would now be recommended. We reached agreement that they would obtain additional safety experience at these higher doses, i.e., about 150-200 overall, including 50 elderly, with a focus on careful orthostatic monitoring.

-Recoding of Verbatim Terms: They agreed to do this, and to focus in particular on events suggestive of hypotension.

-Additional Tyramine Challenge Data: They agreed to conduct an additional study.

-PPA Study Report: They agreed to resubmit the full report for this study.

-TCA, MAOI, and SSRI Contraindication: They argued that Eldepryl and the proposed STS labeling are

we acknowledged this fact.

-Free T4 in Future Studies: They agreed to this.

-Full Data Sets for Carcinogenicity Studies: They agreed to this.

-Repeat Ames and In Vivo Cytogenetics Assay: They agreed to repeat these.

The NDA was resubmitted on 7-31-03, and we held a filing meeting 8-20-03. The sponsor included results of both the new short-term efficacy trial and also the randomized withdrawal trial. The response was considered a complete response to the NA letter, and there was agreement that it could be filed.

We decided not to take selegiline transdermal system (STS) to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

The CMC review was not completed at the time of completion of this memo, however, at this time, I am not aware of any CMC issues that would preclude the approvability of this drug.

3.0 PHARMACOLOGY

The pharm/tox review was not completed at the time of completion of this memo, however, at this time, I am not aware of any pharm/tox issues that would preclude the approvability of this drug.

4.0 BIOPHARMACEUTICS

The pharmacokinetics of selegiline transdermal system (STS) have been adequately characterized and there are no pharmacokinetic deficiencies that would preclude the approvability of this drug.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of New Studies Pertinent to Efficacy

As noted above, there were a total of 4 short-term, placebo-controlled trials of selegiline transdermal system (STS) in major depressive disorder submitted in the original NDA, and we were in agreement with the sponsor on a positive outcome for only 1 of these studies (i.e., E106). In their 7-31-03 response to our NA letter, the sponsor has submitted the results of an additional short-term study (P0052) and a randomized withdrawal study (P9806). These 2 studies were the focus of the efficacy review for this resubmitted NDA, and were reviewed by Greg Dubitsky, M.D., from the clinical group, and by Tristan Massie, Ph.D. from the biometrics group.

5.1.2 Summary of Studies Pertinent to Efficacy Claims

5.1.2.1 Study S9303-P0052

This was a randomized, double-blind, parallel group, 8-week, flexible-dose study (3 US sites) comparing STS (20mg/20cm² to 40mg/40cm², qd) and placebo in adult outpatients meeting DSM-IV criteria for MDD. Patients were started on a dose of 20 mg/20 cm² for the first 2 weeks; based on efficacy and tolerability, the dose could be increased to 30 mg/20 cm² at this point, and the dose could finally be increased to 40 mg/20 cm² after 3 additional weeks. There were roughly 130 patients per each of the 2 groups in the sample analyzed (n=257; n=129 for STS and n=128 for placebo), with the % completing to 8 weeks ranging from 76 to 80%. The patients were about 56% female, about 80% Caucasian, and the mean age was 42 years. The mean STS dose for completers was 35 mg.

While the assessments included MADRS, HAMD-28, CGI, and others, the primary outcome was change from baseline to endpoint in HAMD-28 total score, and I will comment primarily on that outcome. The analysis focused on a modified ITT population, i.e., randomized patients who received at least 1 dose of assigned treatment and who had baseline and at least 1 followup assessment. The LOCF analysis was considered primary, but OC was also done. 2-way ANCOVA was the statistical model employed, with terms for treatment, center, and treatment-by-center interaction. The overall analysis for HAMD-28 was significant (p=0.033):

Efficacy Results on HAMD-17 Total Score for S9303-P0052 (LOCF)

	Baseline HAMD-28	?Baseline HAMD-28	[P-value(vs pbo)]
STS 20-40mg/20-40cm2	28.3	-11.1	0.033
Placebo	28.6	-8.9	

While not described here, results on various secondary endpoints also favored STS over placebo as did the OC analyses.

Comment: Both Drs. Dubitsky and Massie considered this a positive study, and I agree.

5.1.2.2 Study S9303-P9806

This was a 29 center study (all US sites), having the usual design for long-term efficacy, i.e., patients “responding” to open treatment for an acute episode were randomized to continuation on drug or placebo and observed for time to relapse. This trial recruited adult outpatients (≥ 18) who met DSM-IV criteria for major depressive disorder. There was a 10-week open label phase during which all patients received STS 20mg/20cm2 daily. Response was defined as a HAMD-17 total score of ≤ 10 at week 8 or 9 and week 10. Responders were randomized to continuation on STS 20mg/20cm2 daily or were switched to placebo (1:1). There was a 52 week period of observation for relapse. Patients were considered to have relapsed if they met the following criteria at 2 consecutive visits, 2 weeks apart:

-HAMD-17 ≥ 14

-CGI-S ≥ 3 (with at least 2 point increase from double-blind baseline)

-Meeting criteria for DSM-IV MDD

-Note: Patients who needed alternative medication prior to the 2 week followup visit were considered to be discontinued due to lack of efficacy rather than having relapsed.

The primary outcome was cumulative proportion relapsed at 12 months. The statistical model used was Mantel-Haenszel stratified by center. The sample used was a modified ITT sample, i.e., all randomized patients who received at least 1 dose of assigned treatment and who were assess at baseline and at least 1 followup time. As a secondary analysis, the sponsor looked at survival curves that were estimated using Kaplan-Meier methodology; the Cox proportional hazards model was used to compare survival distributions.

There was an excess of females compared to males (about 69%), the mean age was about 43, and patients were predominantly white (about 83%). The mean baseline HAMD-28 at initiation of open treatment was 31, and it was about 7 at the start of double-blind treatment.

A total of n=674 patients were treated during the open label phase, and of these, n=322 met responder criteria and were randomized into the double-blind phase (n=159 to STS and n=163 to placebo). The average time in responder status for these n=322 patients prior to randomization was about 25 days. The intent-to-treat sample included a total of n=312 patients (n=149 for STS and n=163 for placebo).

The overall rates of discontinuation prior to reaching the 52 week endpoint were as follows:

STS: 125/158 (79%)
Placebo: 135/163 (83%)

The results on the primary endpoint, proportion relapsed by 52 weeks, favored STS over placebo:

STS: 21/149 (14%)
Placebo: 39/163 (24%) $p = 0.0183$

The Cox proportional hazards analysis of survival curves also favored STS over placebo:

Hazard ratio (STS vs placebo) = 0.564 ($p = 0.0347$)

The above analyses are based on a strict interpretation of the protocol specified relapses. However, Dr. Dubitsky has noted that 71 additional patients met HAM-D and CGI criteria for relapse at an initial visit, but were then never seen for a second visit in the specified time frame. Some of these patients might reasonably be considered to have had relapses:

- Nine of these patients were ultimately considered to have had relapse by the investigator, despite not having the second confirmatory visit.
- Seventeen patients were considered to be discontinued due to "lack of efficacy"
- Seventeen patients did have confirmatory visits, and met criteria for relapse, but earlier than permitted under the protocol.

Thus, 43 of these 71 patients might be considered to have met criteria for relapse. If they are added to the other relapsed patients for analysis, the results are still significant, both for the proportion relapsed analysis ($p=0.0044$) and the analysis of survival curves ($p=0.0158$).

Comment: Both Drs. Dubitsky and Massie considered this a positive study in support of a claim of longer-term efficacy for STS in MDD, and I agree. Since the run-in period for this study was quite brief (average time in responder status only about 25 days), the study contributes relatively little information on duration of effect.

5.1.3 Comment on Other Important Clinical Issues Regarding Selegiline Transdermal System (STS) for MDD

Evidence Bearing on the Question of Dose/Response for Efficacy

Of the 5 studies reviewed, only study E114-98B was of fixed dose design, and that was a negative study. While we had encouraged the sponsor to conduct a fixed dose study as the additional study, we did not require such a study, and in fact, reached agreement on the planned flexible dose study. Consequently, there is no evidence pertinent to dose response in this program.

Clinical Predictors of Response

Exploratory analyses were done to detect subgroup interactions on the basis of gender, age, and race in a pool of all 5 short-term MDD studies. While there were apparent differences by demographic subgroup, except for race, drug was at least numerically favored over placebo for most of these subgroups. Given the small non-Caucasian subgroup, it is difficult to interpret the reversal in that case. Differences in the placebo effect seem to account for the differences, and the STS effect is actually remarkably consistent across groups.

Size of Treatment Effect

The effect sizes as measured by difference between drug and placebo in change from baseline in the HAM-D-17 observed in study E106-96B and for HAM-D-28 in P0052, the two positive studies, were relatively small, but not unlike those seen in other positive antidepressant trials.

Duration of Treatment

Study P9806 provides some information of maintenance effectiveness. Unfortunately, the run-in period for this study was so brief that the study contributes relatively little information on duration of effect, and this limitation will be noted in labeling.

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided sufficient evidence to support the claim of short-term antidepressant efficacy for STS, and also some limited information on maintenance efficacy.

5.2 Safety Data

5.2.1 Clinical Data Sources for Safety Review

The safety data for the original STS were reviewed by David Gan, M.D., Gerard Boehm, M.D., and Judith Racoosin, M.D., all from the safety group, and Greg Dubitsky, M.D., from the psychopharmacology group. This review was based on an integrated database (with a cutoff date of 7-1-01 for both the integrated database and also for deaths and other serious events). Approximately 2000 human subjects were exposed to STS in the sponsor's development program (in the integrated database) at the time of the original NDA, including 630 in 36 phase 1 studies approximately 1397 in 13 phase 2-3 studies. The various indications studied in the phase 2-3 studies included depression, Parkinson's disease, ADHD, and HIV-associated cognitive impairment. The total person-time for STS-exposed patients in the phase 2-3 depression program was approximately 86 person-years. Patients in phase 2-3 depression studies were roughly 2/3 female, predominantly Caucasian, and the median age was 42.

The following additional data have been accumulated since the original submission:

- 3 phase 1 studies involving n=72 additional STS exposures
- The new short-term efficacy study: P0052
- The new randomized withdrawal study: P9806
- Data from 2 ongoing studies in MDD: P0158 and P0204
- Data from an open label compassionate use study: P0043
- Data from studies in other indications

Thus, the safety data available at this point in time include:

- A total of n=702 STS exposures in phase 1 studies
- A total of n=2,761 STS exposures in phase 2-3 studies (The sponsor has created several pools under this broad category, including Pool A for the 5 short-term efficacy studies (n=817) and Pool B for the larger group of MDD studies (n=2,036). The demographics of Pool A are as follows: mean age about 42; 62% female; about 85% Caucasian. Pool B was similar, but slightly older, with n=198 \geq 65. About 1600 of the roughly 2000 Pool B patients received a dose of 20mg/20cm²; A total of n=273 received a dose of 40mg/40cm², including n=116 who received this dose for \geq 12 weeks.

Since the resubmitted NDA on 7-31-03 included an ISS that was based on a complete recoding of AEs, there was a need for a very extensive re-review of safety data, including a review of all adverse event tables for labeling.

Also, as noted above, there were several specific issues for which we sought additional data, etc. from the sponsor.

5.2.2 Adverse Event Profile for Selegiline Transdermal System (STS)

5.2.2.1 Overview

Recoding Effort

All previous coding was reassessed, and recoding was done for inconsistently or incorrectly coded terms. Dr. Dubitsky has reviewed this effort, and has concluded that coding has now been done in a satisfactory manner.

Adverse Event Profile for STS

For Pool A, only 1 adverse event emerged as common and STS-related using our usual standard (\geq 5% for drug and \geq twice placebo), i.e., application site reaction (24% vs 12%). However, in the only study using higher doses (P0052), several more events emerged as STS-related: insomnia; diarrhea; pharyngitis; back pain.

5.2.2.2 Specific Adverse Events of Concern for Selegiline Transdermal System (STS), and Other Safety Related Issues

5.2.2.2.1 Potential for "Cheese Reaction"

The sponsor conducted a tyramine challenge study at a dose of 40 mg STS out to 90 days. The trend for a decrease in tyramine pressor dose up to 30 days was confirmed, however, there was no further decline beyond 30 days, thus providing reassurance that pharmacodynamic steady state had been achieved. The sponsor also notes that they have now provided safety data in over 2000 patients exposed to 20mg/20cm², and over 400 patients exposed to 30mg/20cm² or 40mg/40cm², all without dietary restriction and all without a single documented case of hypertensive crisis. Finally, they have submitted the full report of the PPA interaction study which also reveals no signal for an interaction. Thus, they argue that there is no need for dietary restriction in 20mg/20cm² to

Comment: Dr. Dubitsky and Dr. Kapcala, the medical officer for oral selegiline, have approached this issue somewhat differently, i.e., looking at the proportion of patients who have a pressor dose close to 40 mg (the amount of tyramine in a tyramine-rich meal). While the pressor dose was somewhat above 40 mg in fed patients, a substantial proportion of fasted patients did have pressor doses at or below 40 mg. Dr. Kapcala also pointed out the considerable intrasubject variability in pressor doses. For these reasons, Dr. Dubitsky argues for dietary restrictions, despite the clinical experience without such restrictions. I think this is a close call, however, I think at least as an initial position we can argue for such restrictions. Regarding the potential for a PPA interaction, Dr. Dubitsky notes that, while an interaction was not observed based on mean change data, outlier analyses did suggest that some patients with the combination may be at risk of substantial blood pressure increases.

5.2.2.2.2 Hypotension

The sponsor did conduct analyses focused on adverse events suggestive of postural hypotension, both for the pool of depression studies and for the pool of Alzheimer's disease studies. They did find that such events were dose dependent in both pools, but somewhat more prominent in the elderly population. Thus, they have proposed general language suggesting such a relationship, and

Comment: I agree with a Precautions statement, however, I think it would be reasonable to recommend orthostatic testing in the elderly.

5.2.2.2.3 Thyroid Function

For Pool A, 3% of STS patients met a criterion for high T4 vs 0.8% for placebo. The sponsor obtained free T4 levels in 2 trials. These data were obtained in study P0052 for only 47 patients, and only for last visit, since that study was already completed. Nevertheless, none of the values were outside the reference range. Free T4 levels were also obtained in open label trial P0204, at baseline

and on treatment. There were no baseline vs on treatment differences, and no values outside the reference range.

Comment: I agree with Dr. Dubitsky that these findings suggest that the slight increase in total T4 is likely due to increased protein-bound hormone.

5.2.2.2.4 Sexual Dysfunction

While the sponsor agrees that the sensitivity of the MED-D scale has not been established, they

5.2.2.2.5 Reports of Serotonin Syndrome

There were 2 reports of serotonin syndrome. One was a patient who overdosed on ephedrine-containing diet pills and 400 mg of amitriptyline while wearing 2 40mg/40cm² STS patches. He was also in possession of a prescription for bupropion 100 mg tid. The other case was a patient who experienced symptoms suggestive of serotonin syndrome after starting venlafaxine within a week of discontinuing STS 40mg/40cm².

5.2.2.2.6 Mania

In Pool A, the risk of manic reaction was 0.2% (2/817) for STS compared to 0.1% (1/668) for placebo. For Pool B, the overall risk of manic reaction was 0.4% (8/2036).

5.2.2.2.7 Application Site Reaction

In Pool A, the risk of ASR was 24% for STS vs 12% for placebo. In study P0052, the risk of ASR was 40% for STS vs 20% for placebo. ASRs were mostly mild or moderate. Dropouts for ASRs were 2% for STS vs 0% for placebo.

5.2.2.3 Conclusions Regarding Safety of Selegiline Transdermal System (STS)

I agree with Dr. Dubitsky that all of the safety issues for this drug can be adequately addressed in labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling.

6.0 WORLD LITERATURE

The sponsor provided an updated literature search with a cutoff date of September, 2003. No important new safety information was revealed in this updated search.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, STS is not marketed anywhere at this time. We will ask for an update on the regulatory status of STS in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We decided not to take this application to the PDAC.

9.0 DSI INSPECTIONS

Inspections were conducted at 2 sites, 1 from study P0052 (Karl Rickels) and 1 from study P9806 (Neil Kaye). Both sites were classified as NAI, and, thus, data were judged to be acceptable from both sites.

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling

We have included a modified version of labeling with the approvable letter.

10.2 Foreign Labeling

STS is not marketed anywhere at this time.

10.3 Approvable Letter

The approvable letter includes our proposed labeling and requests for a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Somerset has now submitted sufficient data to support the conclusion that STS is effective and acceptably safe in the treatment of MDD. Thus, I recommend that we issue the attached approvable letter along with our proposal for labeling, in anticipation of final approval.

cc:

Orig NDA 21-336 (Selegiline Transdermal System [STS])

HFD-120

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

/s/

Thomas Laughren
1/16/04 03:42:48 PM
MEDICAL OFFICER

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA#: 21-336
Sponsor: Somerset Pharmaceuticals
Due Date: February 1, 2004

Drug Name:

Generic Name: Selegiline Transdermal System
Trade Name: EMSAM

Drug Categorization:

Pharmacological Class: MAOI
Proposed Indication: Depression
Dosage Forms: 20mg, 30mg, and 40mg Patches
Route: Transdermal

Review Information

Clinical Reviewers: Gregory M. Dubitsky, M.D.
Completion Date: December 16, 2003

NDA 21-336
SELEGILINE TRANSDERMAL SYSTEM FOR DEPRESSION
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EXECUTIVE SUMMARY

I. Recommendations

A. Approvability

The sponsor has presented adequate information to show that STS is reasonably safe and efficacious in the acute and longer-term treatment of major depression in 20mg/20cm², 30mg/30cm², and 40mg/40cm² daily patches.

From a clinical perspective, it is recommended that this application be approved with the labeling changes delineated in **section IX** and a Medication Guide in accordance with 21 CFR 208.20 to insure that each patient is provided with information regarding a tyramine-restricted diet.

B. Recommendations for Phase 4 Studies

There are no clinical recommendations for Phase 4 studies.

II. Summary of Clinical Findings

A. Brief Overview of the Submission

This submission is intended to provide a full response to our non-approvable letter dated 3-25-02. See **section I.A** of the clinical review below for further information.

It contains the study reports of 3 new Phase 1 trials:

- P0051 - a PK study of alternate STS application sites.
- P0156 - a study of the effect of STS on the extent of systemic MAO-A and MAO-B inhibition.
- P0201 - a long-term tyramine challenge study.

Additionally, the study reports for 2 new efficacy trials, P0052 and P9806, are provided in this submission. Study P0052 provides evidence of acute efficacy to supplement efficacy data from study E106-96B, which was presented in the original submission of this NDA. Study P0052 utilized higher daily doses of STS (up to 40mg/40cm²) compared to the previously reported trials, which used a maximum dose of 20mg/20cm². Study P9806 is a relapse prevention trial conducted in patients who attained remission after 10 weeks of open-label treatment with STS 20mg/20cm² daily.

C. Safety

The sponsor has adequately responded to the safety concerns conveyed in the 3-25-02 NA letter.

The safety review of this submission revealed the following notable findings:

- application site reactions (ASR's) are common, drug-related events. Most ASR's were mild or moderate in severity and consisted of erythema, edema, and/or papules. None were considered serious. Few patients dropped out due to ASR's. See **section VII.B.5** for details.
- there were a greater number of common, drug-related adverse experiences in study P0052, which utilized higher mean doses of STS, than in the pool of all short-term, placebo-controlled, depression trials (Pool A), where mean doses were considerably lower. See **section VII.B.4** for details.
- tyramine pressor doses decreased considerably within the first month of treatment with STS 40mg/40cm² per day in study P0201. However, there were no further appreciable decreases after the second and third months of such treatment. Nonetheless, the apparent margin of safety observed in this study was not large. I feel that dietary restrictions should be exercised during and for 2 weeks after STS therapy. Please see **section VII.B.9** for further information and discussion.
- Study P0046, which examined the potential for STS to potentiate blood pressure and heart rate elevation secondary to phenylpropanolamine (PPA), produced no clear evidence of a pharmacodynamic interaction between PPA and STS in terms of mean maximal changes in blood pressure and heart rate. However, there were a greater number of patients with pressor responses during combined STS plus PPA exposure compared to either drug alone, suggesting that some patients who receive both drugs concurrently may experience large increases in systolic blood pressure. See **section VII.B.9** for details.
- There were two cases of possible serotonin syndrome classified as serious adverse events: one occurred when a suprathreshold dose of STS was taken with an overdose of nortriptyline and ephedrine and the second when venlafaxine was taken a week after discontinuing STS. Please see **section VII.B.2** for details. These cases suggest that some patients may experience serious adverse events due to pharmacodynamic interactions between STS, on the one hand,

and sympathomimetic drugs, TCA's, or SNRI's, on the other hand.

Overall, there were no safety findings that would, in my opinion, preclude approval of STS in the daily doses of 20mg/20cm², 30mg/30cm², or 40mg/40cm² for the treatment of major depression.

D. Dosing

On the whole, data suggest that the daily application of STS patches of 20mg/20cm², 30mg/30cm², and 40mg/40cm² are reasonably safe and effective in the treatment of major depression. No reliable dose-response information is available.

CLINICAL REVIEW

I. Background

A. Administrative History

Selegiline is a monoamine oxidase inhibitor (MAOI) which has been developed as a transdermal patch formulation (Selegiline Transdermal System or STS) for the treatment of major depression. 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.²

Accordingly, this NDA was declared non-approvable (NA) due to insufficient evidence of efficacy and an action letter was issued on 3-25-02. This letter also delineated a number of other clinical, non-clinical, and chemistry, manufacturing and controls issues which would be appropriate to be addressed along with the efficacy deficiency should Somerset choose to amend their application in response to the NA letter. The clinical areas of concern are discussed in the following section.

A 4-22-02 teleconference and a 5-2-02 meeting were held with Somerset to discuss the deficiencies communicated in

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

the NA letter and the sponsor's planned response to the NA action.³

The current submission, dated 7-31-03, contains the sponsor's response to our NA letter. The Division review team met on 8-20-03 and agreed that this submission contained an adequate response to the NA letter. The action due date is 2-1-04.

B. Clinical Issues from NA Letter

1. Reason for the NA Action

The reason for our non-approvable action was lack of evidence of efficacy from more than one adequate and well-controlled study.

In the original NDA, Somerset had presented efficacy data from a total of four short-term, placebo-controlled trials of STS in major depression (E106-96B, P9804, E114-98B, and E113-98B). At that time, the sponsor purported that two of these trials were positive (E106-96B and P9804) while acknowledging that two (E114-98B and E113-98B) were negative.

Our NA letter notes that the study reports for all four trials presented efficacy analyses based on a patient sample which is not acceptable to the Agency, i.e., all randomized patients who received at least one dose of assigned treatment and had a baseline assessment, regardless of whether a post-baseline assessment on the primary efficacy variable was available; where it was not available, baseline scores were carried forward as imputed post-baseline measures.

Nevertheless, we concurred that study E106-96B was positive and that studies E114-98B and E113-98B were negative. After a reanalysis of study P9804 utilizing the acceptable patient sample (all randomized patients who received at least one dose of assigned treatment and who had both a baseline score and at least one post-baseline score on the primary variable), STS was not found to be superior to placebo ($p=0.069$). Furthermore, after excluding age as a covariate in the statistical model in accordance with the latest amended protocol for this trial, the efficacy

³ See "Minutes of Meeting with Firm" signed by Russell Katz, M.D., on 6-11-02.

results were even weaker (p=0.084). Hence, study P9804 was deemed negative, leaving study E106-96B as the sole positive trial.

This was not regarded as sufficient evidence of efficacy. We did indicate that we would consider one additional positive study both necessary and sufficient to demonstrate the efficacy of STS for major depression. We also conveyed our feeling at that time that it was critical to examine several fixed doses of STS in the next study, given the preponderance of negative results for the 20 mg/day dose in the above studies.

Somerset has responded to this deficiency by conducting an additional short-term, placebo-controlled trial using flexible dosing in the range of 20-40 mg/day (study P0052). The results of this study are reviewed in **section VI.A** of this review.

2. Other Clinical Concerns Conveyed in the NA Letter

1) Proprietary Name (EMSAM)

The sponsor was reminded that their proposed proprietary name, EMSAM, would have to be reevaluated about 90 days prior to the expected approval of the application.

2) Problems in Adverse Event Coding

Serious problems had been detected in the coding of adverse events in the original NDA. These problems were felt to compromise the entire safety database and necessitated recoding of all verbatim adverse event terms. This concern is addressed in **section VII.B.4**.

3) Potential for "Cheese Reaction"

Tyramine challenge studies presented in the original NDA suggested that the tyramine pressor dose tended to decrease with the duration of STS administration. Since STS would be intended for chronic use, we asked the sponsor to repeat tyramine challenge testing after 60 days of use and, if indicated, at later time points as well. In response, Somerset conducted study P0201 which examined tyramine pressor doses after 30, 60, and 90 days of STS 40 mg/day. This study is reviewed in **section VII.B.9**.

Furthermore, summary data from the phenylpropanolamine (PPA) interaction study (P0046) in the original NDA indicated mean increases in blood pressure of 8-10 mmHg

associated with the co-administration of PPA and STS compared to PPA alone. To further evaluate the results of this study, we requested the full report of this study. The study report had been submitted on 4-5-02 and was examined. This study is discussed in **section VII.B.9.**

4) Potential Interaction with TCA's and SSRI's

Somerset was advised that,

STS would be contraindicated with TCA's and SSRI's. It was our impression that the currently marketed oral formulation of selegiline (Eldepryl) was contraindicated with TCA's and SSRI's. Somerset responded that, in fact, Eldepryl labeling does not contraindicate such co-administration but advises against it in a statement contained in the WARNINGS section of labeling. No further data relevant to the potential interaction between STS and TCA's or SSRI's has been presented by the sponsor.

5) Adverse Events Related to Postural Hypotension

It was noted that, in the original NDA database, there was no apparent excess of adverse experiences possibly related to orthostatic hypotension despite a finding of orthostatic changes in STS-treated patients based on vital sign measurements. We asked the sponsor to review the reporting rates of such events within the pool of controlled depression studies after the recoding of adverse events as discussed above. The relevant data are presented in **section VII.B.7.**

6) Thyroid Function

A finding of elevated total T4 levels was noted in the original NDA safety database. We indicated that future studies should include a measurement of free T4 levels to further evaluate this finding. The protocols of two ongoing studies (P0052 and P0204) were amended to measure free T4 levels. The results are discussed in **section VII.B.6.**

7) Sexual Dysfunction

Apparently a slight improvement in sexual functioning associated with STS was noted in previously submitted depression trials based on the mean change in a subset of five items from the MED-D scale. The sponsor had

/ / - / / /

The sponsor acknowledges that the sensitivity of the MED-D has not been established and they present no more rigorous data. Thus, this issue is not further addressed in this review.

II. Clinical Findings from Consultant Reviews

A. Statistical Review and Evaluation

The statistical reviewer is Tristan Massie, Ph.D. The statistical review of this submission is currently pending completion. Dr. Massie was consulted on several occasions during my review of the new efficacy data. It is my understanding that he and I are in basic agreement regarding interpretation of the new, key efficacy trials, P0052 and P9806.

B. DSI Site Inspections

The Division of Scientific Investigations (DSI) was consulted on 10-22-03 to inspect 2 clinical sites, one from study P0052 and one from study P9806. These inspections are pending at this time.

C. Clinical Pharmacology and Biopharmaceutics

Ron Kavanagh, Pharm.D., Ph.D., is the biopharmaceutics reviewer for this NDA. His review is pending completion at this time. He has informally provided me with preliminary information based on his review thus far. Clinically relevant information has been incorporated into this review.

D. Chemistry

Donald Klein, Ph.D., is the chemistry reviewer assigned to this NDA. His review is not yet complete. On 12-11-03, he verbally informed me that there were no major clinically relevant chemistry problems as of that date.

E. Nonclinical Pharmacology and Toxicology

Paul Roney, Ph.D., is the nonclinical pharmacology reviewer for this NDA. He has not yet completed his review. On 12-11-03, he verbally informed me that he was aware of no clinically relevant pharmacology/toxicology problems.

F. Microbiology

The microbiology reviewer is Stephen Langille, Ph.D. He completed his review on 11-12-03 and recommended approval from the standpoint of microbial product quality.

G. DMETS

The Division of Medication Errors and Technical Support (DMETS) stated in their 1-24-02 consultation response that there was no objection to the proprietary name, EMSAM. This response also conveyed the following recommendations regarding the product packaging and labeling to minimize potential user error:

Patch Label

Printing the "EMSAM 20" image on the patch itself, as opposed to the removable protective backing, would increase visibility of the patch, making location of the patch and removal easier. (Postmarketing experience with clear transdermal patches has resulted in medication errors.)

Pouch Labeling

The phrase "upper torso" should be revised to "upper torso (below the neck and above the waist)" to facilitate patient understanding.

Carton Labeling

See the above comment regarding the Pouch Labeling.

If space permits, the use of an illustration for handling and applying the patch would enhance patient understanding.

Package Insert

Under PRECAUTIONS/Information for Patients:

- Information should be repeated at the end of the insert in accordance with 21 CFR 201.57(f)(2).
- See the above comment regarding an illustration.
- Increase the prominence of the statement ' _____' in instruction 2.
- All instructions should be consistent with those on the Carton and Container.
- Increase the prominence of the phrase "Wash your hands" in instruction 6 and 9.

Under DOSAGE AND ADMINISTRATION:

- See the above comment regarding the Pouch Labeling.
- Include the "How to Use EMSAM" section from PRECAUTIONS in this section.

Given the length of time since that response, the proprietary name was reevaluated recently by DMETS. According to verbal information from the Project Manager, Doris Bates, on 12-11-03, the name EMSAM has again been found to be acceptable.

III. Human Pharmacokinetics and Pharmacodynamics

A. Human Pharmacokinetics

The sponsor completed one new pharmacokinetic study since the original submission of this NDA. Study P0051 was a randomized, open-label, 6-way, 3-treatment, 3-period crossover study of selegiline pharmacokinetics resulting from 3 alternate patch application sites in 27 normal volunteers. The study report will be reviewed by the biopharmaceutics reviewer, Dr. Ron Kavanagh.

Somerset reports that bioequivalence between these application sites was shown. However, Dr. Kavanagh informed me of his conclusions from this study in an informal communication on 12-9-03: patch application to the upper thigh is bioequivalent to application to the upper torso but application to the upper buttock is not bioequivalent to application to the upper torso and upper thigh. Higher selegiline concentrations were observed after application to the upper buttocks. No bioequivalence data was provided for application to the upper arm.

Dr. Kavanagh also informed me that the mean delivery rate of selegiline for the 40mg patch applied to the torso was 12mg per day. Selegiline exposures after transdermal application of this patch are approximately 20-fold higher than after a roughly comparable oral dose (10mg), with metabolite exposures about one-third lower than after oral administration. Given this considerably higher exposure with the patch, he does not feel that reliance on the safety data from the oral formulation is appropriate for assessing the safety of the STS patch. In fact, the safety assessment of the STS patch does not rely on experience with the oral formulation to any appreciable extent.

B. Pharmacodynamics

The sponsor completed one new pharmacodynamic study (P0156) which examined the effects of STS on MAO-A and MAO-B inhibition. This investigation is summarized below.

Study P0156 (Effect on MAO-A & MAO-B Inhibition)

Study Design

This was a single-center, open-label, multiple dose, parallel group investigation of systemic MAO-A and MAO-B activity after application of three different STS doses in 25 healthy male volunteers.

Subjects were randomized to one of three treatments: STS 20mg/20cm² (Group 1, N=9), STS 30mg/30cm² (Group 2, N=8), or two patches of STS 20mg/20cm² (Group 3, N=8). All doses were placed on the upper torso every 24 hours for 10 days (study Days 2-11). Study days 3-9, inclusive, were done on an outpatient basis. Subjects were cautioned not to take any concomitant medications without permission from the investigator; no such usage was reported during the trial. The study was conducted without dietary tyramine restrictions.

Assessments included:

- blood samples for platelet MAO determination on Day 1, prior to dosing on Days 2 and 11, and prior to STS removal on Day 12;
- two 24 hour urine samples for MHPG and PEA determinations (Days 1 and 11).

Human platelets contain only MAO-B and, thus, platelet MAO activity is often used as a surrogate marker for systemic MAO-B activity. In this study, platelet MAO activity was measured using ^{14}C -PEA as a substrate.

MHPG (3-methoxy-4-hydroxyphenylglycol) is a major metabolite of CNS and peripheral norepinephrine, which is metabolized extensively by intraneuronal MAO-A. Thus, urine or plasma MHPG is used as a surrogate marker of MAO-A activity in the CNS and peripheral sympathetic nervous system.

PEA (phenylethylamine) is a specific substrate for MAO-B and its concentration in urine or plasma is used as a surrogate marker of inhibition of brain MAO-B activity.

Study Results

Platelet MAO-B activity was significantly reduced from baseline in all three dose groups, with greater than 99.6% inhibition in each.⁴

The decrease from baseline in urinary MHPG excretion was significantly greater in the two high dose groups (-29.7% in the 30mg/30cm² group and -49.5% in the 2 x 20mg/20cm² group). A linear regression analysis showed a statistically significant inverse relationship between urinary MHPG excretion and STS dose ($p=0.004$, $R^2=0.32$).

The increase from baseline in urinary PEA excretion was large in all 3 treatment groups (greater than 40-fold), with no significant relationship to dose.

There were no serious adverse events or dropouts due to adverse events in this trial.

In sum, this study appears to demonstrate potent and complete inhibition of MAO-B by all STS doses examined. Results suggest that STS inhibits MAO-A in a dose-dependent manner.

⁴ Percent inhibition=[Change in activity/Baseline activity] x 100%.