CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-336/21-708

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
21336 and 21708

NAME OF APPLICANT / NDA HOLDER
SOMERSET PHARMACEUTICALS, INC.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
EMSAM

ACTIVE INGREDIENT(S)	STRENGTH(S)
SELEGILINE	20 mg

DOSAGE FORM
TRANSDERMAL

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
RE34,579	04/05/1994	08/18/2007

d. Name of Patent Owner	Address *(of Patent Owner)*	
SOMERSET PHARMACEUTICALS, INC.	2202 N. WEST SHORE BLVD., SUITE 450	
	City/State: TAMPA FLORIDA	
	ZIP Code: 33607	FAX Number *(if available)*: (813) 282-3804
	Telephone Number: (813) 288-0040	E-Mail Address *(if available)*: mlg@somersetpharm.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
☞ N/A	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☑ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☑ No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☑ No
2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☑ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☑ No
2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☑ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☑ No
3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☑ Yes	☐ No

4.2 Claim Number (*as listed in the patent*)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?		
1, 2, 3, 4, 5, AND 6		☑ Yes	☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)* MAJOR DEPRESSIVE DISORDER AND MAINTENANCE TREATMENT OF MAJOR DEPRESSIVE DISORDER

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Margaret Sampson	5-25-05

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☑ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name MARGARET J. SAMPSON	
Address 2801 VIA FORTUNA, SUITE 100	City/State AUSTIN, TX
ZIP Code 78746	Telephone Number (512) 542-8659
FAX Number *(if available)* (512) 236-3264	E-Mail Address *(if available)* msampson@velaw.com

EXCLUSIVITY SUMMARY

NDA # 21-336 & 21-708 SUPPL # HFD # 130

Trade Name EMSAM

Generic Name Selegiline

Applicant Name Somerset

Approval Date, If Known 2-27-06

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-334 Eldepryl

NDA# 20-647 Eldepryl

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

P0052 and E106-96B provide evidence of acute efficacy in MDD patients. Study P9806 provided evidence of long-term efficacy in MDD patients.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☒	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA 21-336: 0052 and E106-96B provide evidence of acute efficacy in MDD patients.

NDA 21-708: Study P9806 provided evidence of long-term efficacy in MDD patients.

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 46,994	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Renmeet Gujral, Pharm.D.
Title: Regulatory Project Manager
Date: 2-22-06

Name of Office/Division Director signing form: Thomas Laughren, M.D.
Title: Division Director, DPP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

DEBARMENT CERTIFICATION

May 25, 2005

Somerset Pharmaceuticals, Inc. hereby certifies that it did not and will not use, in any capacity, the services of any person debared under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signed: Melissa L. Goodhead Date: 25 May. 2005.

Melissa L. Goodhead, B.Sc., RAC
Group Director, RA/QA

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-336/ 21-708	Efficacy Supplement Type SE-	Supplement Number	
Drug: EMSAM		Applicant: Somerset Pharmaceuticals Inc.	
RPM: Renmeet Gujral, Pharm.D		HFD-130	Phone # 301-796-1080

Application Type: **(X)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	2020100
• Other (e.g., orphan, OTC)	3
❖ User Fee Goal Dates	
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(x) Paid UF ID number 4146
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) N/A
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify) N/A
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	AE(1/30/04), NA (3/25/02)
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	2-21-06
• Most recent applicant-proposed labeling	2-7-06
• Original applicant-proposed labeling	5-25-05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMETS 2-7-06, 9-30-05, 7-15-05 DSRCS 1-31-06, 10-05-05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	2-21-06
• Applicant proposed	2-7-06
• Reviews	DMETS 2-7-06, 9-30-05, 7-15-05
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	Yes
• Documentation of discussions and/or agreements relating to post-marketing commitments	Yes (1-18-06)
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	Yes
❖ Memoranda and Telecons	Yes
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X
• Pre-NDA meeting (indicate date)	X
• Pre-Approval Safety Conference (indicate date; approvals only)	X
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	10-26-05
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	

Summary/Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Division Director
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	1-22-06, 9-21-05
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	draft
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	N/A
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	N/A
❖ Biopharmaceutical review(s) *(indicate date for each review)*	11-3-05, 5-13-05
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	11-8-05
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	
❖ CAC/ECAC report	X

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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

DATE: February 15, 2006

TO: Thomas Laughren, M.D., Director
Division of Psychiatric Products (DPP)

THROUGH: Jonca Bull, MD, Acting Deputy Director
Office of Drug Safety

FROM: ODS EMSAM RiskMAP Team

DRUG: EMSAM™ (selegiline transdermal system)

NDA: 21-336 and 21-708

SPONSOR: Somerset Pharmaceuticals, Inc.

SUBJECT: Review of Risk Management Plan, submitted November 21, 2005

PID: D050658

1 EXECUTIVE SUMMARY

This consult is in response to a request from the Division of Psychiatric Products (DPP) to comment on Risk Management Plan for EMSAM (seligiline transdermal system) as treatment for major depressive disorder (MDD). If approved, EMSAM will be the first seligiline-containing transdermal product available in the U.S.

Selegiline is an irreversible inhibitor of monoamine oxidase (MAO) and is currently available in an oral dosage form in the U.S. (Eldepryl) for the adjunctive management of Parkinsonian patients. The primary "risk" issue is the potential for hypertensive crisis which is a known adverse event associated with MAO inhibitors and dietary tyramine which is found in a variety of foods and drugs. The sponsor feels that data supports at least the 20 mg patch as being relatively free of the risk of the however, there is little data regarding this safety issue for the 30 and 40 mg strengths.

The sponsor has proposed to address the risk issue with a RiskMAP that focuses on education of healthcare providers and consumers regarding the risk with the higher dosage forms (30 and 40mg patches). In general, we agree with the Sponsor's approach to risk minimization but we believe that having different educational messages for different doses of the same medication may be too difficult of a concept for many

patients, especially those with lower literacy level. This document summarizes the Sponsor's RiskMAP and pharmacovigilance proposal and conveys comments and recommendations from the divisions in the Office of Drug Safety on the surveillance and education plan currently proposed by the Sponsors throughout the document and in Section 5.

2 BACKGROUND

EMSAM (selegiline transdermal system) is a transdermally administered antidepressant designed to continuously deliver selegiline over a 24-hour period. The proposed indication for EMSAM is to treat major depressive disorder (MDD). In 2002, a non-approvable letter was issued on the basis of lack of efficacy evidence from more than one adequate and well-controlled study. The sponsor has now presented adequate information and an advisory committee meeting convened on 10/25/05 to consider whether EMSAM can be safely marketed in its 20 mg strength without dietary restrictions but with restrictions for the 30 and 40 mg strengths.

Selegiline is an irreversible inhibitor of monoamine oxidase (MAO) and is currently available in an oral dosage form in the US (Eldepryl) for the adjunctive management of Parkinsonian patients. In the CNS neurons, MAO plays an important role in the catabolism of catecholamines (dopamine, norepinephrine and epinephrine) and serotonin. MAOs are also important in the catabolism of various exogenous amines (e.g., tyramine) found in a variety of foods and drugs. If absorbed intact, exogenous amines have the capacity to cause a 'hypertensive crisis' by gaining access to the systemic circulation and when taken up by adrenergic neurons, norepinephrine (NE) is displaced. Subsequent release of the displaced NE causes a rise in systemic blood pressure and thus, a hypertensive crisis may ensue. The transdermal formulation bypasses the gut wall (theoretically avoiding a substantial inhibition of gut wall MAO-A). The sponsor feels that data supports at least the 20 mg patch as being relatively free of the risk of the "cheese reaction"; however, there is little data regarding this safety issue for the 30 and 40 mg strengths.

Oral selegiline was approved by the FDA in 1989 to treat Parkinson's disease.
On October 26, 2005, the FDA's Psychopharmacologic Drugs Advisory Committee endorsed the safety of 20mg EMSAM to treat MDD, **without** dietary tyramine modifications. However, at the same time, the advisory committee endorsed the use of EMSAM 30 and 40mg to treat MDD, but **with** dietary tyramine modification. The sponsor's Risk Management Plan dated November 21, 2005 was submitted in response to the October 26, 2005 Advisory Committee meeting's recommendations.

Additional safety issues conveyed from Drs. Laughren and Dubitsky to DDRE at a preapproval safety conference included the potential for systemic allergic reactions (e.g., throat constriction, facial edema, and generalized urticaria); psychotic symptoms (e.g., paranoia, delusions, and hallucinations); and skin cancer (e.g., melanoma was seen with similar drug, resagiline, but EMSAM had no signal).

A1

9 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

ODS Emsam RMP Team:
Syed Rizwanuddin Ahmad, M.D., M.P.H., Medical Epidemiologist, DDRE
Jeanine Best, MSN, RN, PNP, Patient Product Information Specialist , DSRCS
Nancy Clark, PharmD., BCPP, Regulatory Project Manager, DSRCS
Mary Dempsey, Project Management Officer, ODS-IO
Jodi Duckhorn, Patient Product Information Specialist TL, DSRCS
Jinhee L. Jahng, Pharm.D., Safety Evaluator (LCDR USPHS)
Claudia B. Karwoski, Pharm.D., Scientific Coordinator, ODS-IO
Cherye Milburn, Regulatory Project Manager, ODS-IO
Alina R. Mahmud, R.Ph., Team Leader, DMETS
Toni Piazza-Hepp, Pharm.D., Acting Director, DSRCS
Marilyn Pitts, Pharm.D, Team Leader Safety Evaluator, DDRE
Sonny Saini, Pharm.D., Safety Evaluator, DDRE

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/s/

Mary Dempsey
2/16/2006 08:02:53 AM
DRUG SAFETY OFFICE REVIEWER

Jonca Bull
2/22/2006 03:30:57 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: 2-21-06

APPLICATION NUMBER: NDA 21-336 & 21-708

BETWEEN:

Name:	Melissa Goodhead
	Mel Sharoke
Phone:	1-888-892-8889 X 276
Representing:	Somerset Pharmaceuticals

AND

Name:	Renmeet Gujral, Pharm.D
	Paul David,
	Division Psychiatry Drug Products, HFD-130

SUBJECT: Confirm PDUFA goal date

This is a telecon to confirm the PDUFA goal date which was relayed to the sponsor in December 2005. In the extension letter it states the due date is February 26, 2006, but the sponsor was contacted in December to let them know the PDUFA due date is February 27, 2006. We confirmed this with the sponsor in a telecon today.

_____

Renmeet Gujral, Pharm.D.
Regulatory Project Manager

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/s/

Renmeet Gujral
2/22/2006 03:09:12 PM
CSO

Office of Drug Safety

MEMO

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

From: Jinhee L. Jahng, Pharm.D.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Alina R. Mahmud, R.Ph., M.S., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Date: November 30, 2005

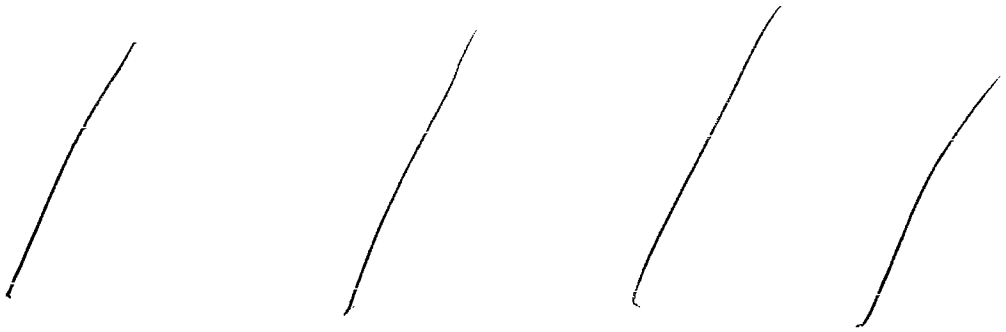
Re: ODS Consult 00-0159-6
Emsam (Selegiline Transdermal System)
NDA 21-336: 20 mg
NDA 21-708: 20 mg; 30 mg, 40 mg;

This memorandum is in response to a November 17, 2005 request from your Division for a re-review of the proprietary name, Emsam (NDA's 21-336 and 21-708) and review of the revised labels and labeling. NDA 21-708 was administratively created to address the maintenance treatment of major depressive disorder, with the acute treatment indication retained under the existing NDA 21-336. The proposed proprietary name was found acceptable by DMETS on September 13, 2000 (ODS Consult #00-0159), January 17, 2002 (ODS Consult #00-0159-1), October 29, 2003 (ODS Consult #00-0159-2), June 20, 2005 (ODS Consult #00-0159-3), and September 14, 2005 (ODS Consult #00-0159-4).

Since the completion of our last consult, DMETS identified two additional proprietary names — and Emcin Clear that may have the potential for confusion with Emsam. However, Emcin Clear was not evaluated further due to a lack of availability of information in common drug information references such as MICROMEDEX, online Facts and Comparisons, Thomson and Thomson's SAEGIS Online Service, Red Book, and the online Orange Book).

— is an NDA (ODS Consult — currently under review at the FDA and is not approved or marketed in the United States at this time.

*** Name pending approval. Not FOI releasable.



. Given the similarities between — and Emsam, DMETS believes that the names may not co-exist in the marketplace since unfamiliarity with either product may increase the potential for a dispensing error to take place should both products be launched around similar dates. Therefore, the application that receives approval first is entitled to the name.

DMETS has attempted to focus on safety issues relating to possible medication errors, and refers you to the recommendations made in ODS Consult 00-0159-5 for Tabs 3-5. We have reiterated some of the comments from the aforementioned review to re-emphasize the suggested recommendations. In regards to Tabs 6-8, DMETS has identified the following areas of possible improvement, which might minimize potential user error.

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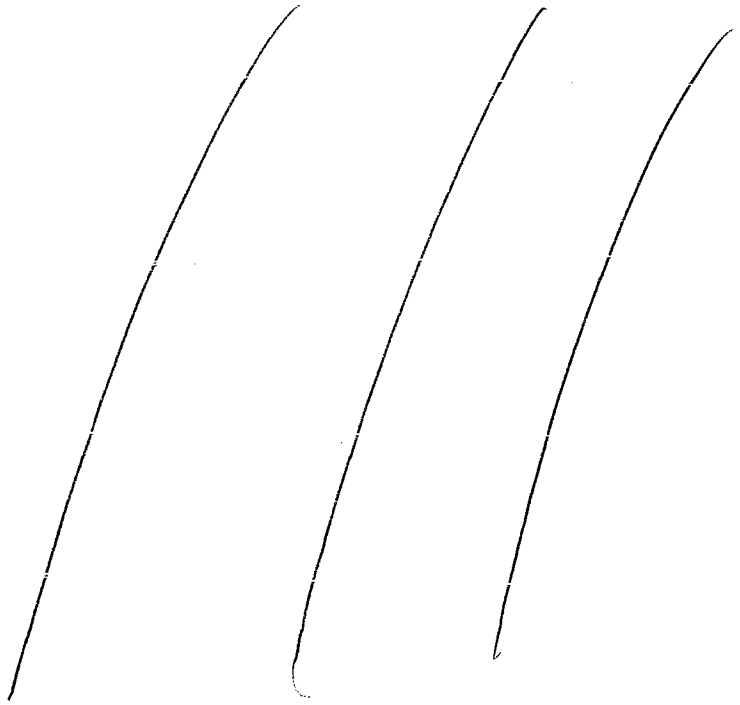

*** Name pending approval. Not FOI releasable.

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_____ Draft Labeling

_____ Deliberative Process

In summary, DMETS has no objections to the use of the proprietary name, Emsam, provided that ***only one name***, Emsam (NDA 21-336/21-708) **or** [redacted] is approved. The acceptability of the proposed proprietary name, Emsam, depends on which application, Emsam or [redacted], receives approval first, as these two names may not coexist in the U.S. market due to their similarities (see page 1). In addition to the label and labeling comments made in this consult, refer to ODS consult 00-0159-5, dated November 2, 2005, regarding recommendations for the labels and labeling of these products.

We consider this a final review. However, if the approval of the NDA's are delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before the NDA's approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

If you have any questions or need clarification, please contact DMETS Project Manager, Diane Smith, at 301-796-0538.

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/s/

Jinhee Jahng
2/7/2006 03:02:10 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
2/7/2006 03:34:05 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/7/2006 03:39:23 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/7/2006 03:45:41 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: January 31, 2006

TO: Thomas P. Laughren, M.D., Director
Division of Psychiatry Products

VIA: Renmeet Gujral, Regulatory h Project Manager
Division of Psychiatry Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review of Medication Guide for Emsam (selegiline transdermal system), NDA 21-336 and 21-708

Background

The sponsor submitted revised labeling, including the required Class Antidepressant Medication Guide expanded to include product specific information for Emsam (selegiline transdermal system), NDA 21-336 and 21-708, as part of a complete response submitted May 26, 2005, amended November 3, 2005, to an Approvable Action taken January 30, 2004.

Attached are our recommended revisions to the proposed expanded Class Antidepressant Medication Guide. We have simplified the wording, made it consistent with the PI, removed unnecessary information, and put it in the format specified for Medication Guides in 21 CFR 208.20. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Medication Guides should always be consistent with the prescribing information. All future relevant changes to the Prescribing Information (PI) should also be reflected in the Medication Guide.

Comments and Recommendations

1. We have made the Medication Guide consistent with the information presented in PI, and agree that awareness of the (higher dose) dietary modifications is extremely important, but we are concerned that having different educational messages for different doses of the same

medication may be too difficult of a concept for many patients, especially those with lower literacy levels. Consideration should be given to revising this information in the PI and MG and provide the WARNING for all EMSAM doses.

2. We have moved the required Class Medication Guide text to the end of the Emsam Medication Guide for the following reasons:

    a. Many patients will fail to read the MG if the Class Antidepressant MG text is the opening information and believe the information does not pertain to them, because of the title "About Using Antidepressants in Children and Teenagers."

    b. EMSAM is not indicated for patients under the age of 18.

We can provide clean and marked-up copies of the document in Word if requested by the review division.

10 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

) *(Division/Office)*:
OPSS/ODS/IO; HFD-400
Attn: Mary Dempsey

FROM:
OND/ODE1/DPP
HFD-130

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/22/05		21-336 & 21-708	Risk MAP	11/21/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
EMSAM		MDD	**PDUFA DATE: 2/26/06**

NAME OF FIRM: Somerset Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Hi Mary,

This is the Risk Map for NDA 21-336 & 21-708 for EMSAM for MDD. The PDUFA due date is February 26, 2006. I know Doris Bates who was the previous Project Manager for these NDA's briefed you. Please let me know if you need anything else. I can be reached at either gujralr@cder.fda.gov or 301-796-1080.

Thanks,
Rimmy

SIGNATURE OF REQUESTER
Renmeet Gujral, Pharm.D.
Regulatory Project Manager
301-796-1080
ujralr@cder.fda.gov

METHOD OF DELIVERY (Check one)
☐ MAIL ☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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/s/

Renmeet Gujral
11/29/2005 04:18:52 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM:
ODS/DMETS/ HFD-420	HFD-130 Division of Psychiatry Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/17/05		21-336 & 21-708	Trademark rereview; extension to the PDUFA clock	NDA resubmission rec'd 11/17/05

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
EMSAM (transdermal selegiline)		antidepressant	**Action Due 2/26/06**

NAME OF FIRM: Somerset Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a resubmission of the trademark EMSAM for consideration, given that the NDA due date has been extended for 3 more months. The new due date for this NDA is February 26, 2006. I have also included your prior reviews on this NDA for reference. If you have any questions, please contact Renmeet Gujral at 301-594-5535 or gujralr@cder.fda.gov.

Thank you

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Renmeet Gujral, Pharm.D. Regulatory Project Manager 01-796-1080 gujralr@cder.fda.gov	x MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Renmeet Gujral
11/18/2005 08:56:23 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-336/21-708

Somerset Pharmaceuticals, Inc.
Attention: Melissa Goodhead, B.Sc., RAC
Group Director of Regulatory Affairs
2202 North West Shore Boulevard #450
Tampa, FL 33607

Dear Ms. Goodhead:

Please refer to your May 24, 2001 new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMSAM (selegiline transdermal system) 20, 30, and 40 mg/cm(2).

Please also refer to your Class 2 Complete Response to our January 30, 2004 action letter. Based on our receipt of this submission, the original user fee goal date for your amended application was November 26, 2005.

On November 16, 2005, we received your major amendment to this application. The major amendment contains information related to the RiskMAP, which was not previously submitted to these NDAs. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 26, 2006.

If you have any questions, please call me at 301-796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
11/18/2005 12:31:22 PM

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

November 4, 2005

Thomas Laughren, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products, HFD-120
Attention: Division Document Room, 4008
VIA Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

RE: NDA 21,336/21,708
EMSAM® (Selegiline Transdermal System)
Correspondence Submission
N:062

Dear Dr. Laughren:

As per my communication with Dr. Doris Bates, enclosed please find copies of two email correspondence, with the Division, regarding the above stated NDAs. This submission is for NDA administrative purposes.

Please do not hesitate to contact me should you require any further documentation.

Sincerely,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc., RAC
Group Director, Regulatory Affairs/Quality Assurance

:mlg

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Somerset Pharmaceuticals, Inc.	October 10, 2005
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(813) 288-0040	(813) 282-3804
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
2202 North West Shore Boulevard Suite 450 Tampa, Florida 33607	

RECEIVED
OCT 11 2005
CDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21,336

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
EMSAM	SelegilineTransdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Transdermal	20mg, 30mg, 40mg	Transdermal

(PROPOSED) INDICATION(S) FOR USE: MDD

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☒ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment Information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*

- ☐ 1. Index
- ☐ 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
  - ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
  - ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(k)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER *(Specify)* Requested CMC Information

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Melissa L. Goodhead	Melissa L. Goodhead Group Director, Regulatory Affairs/QA	10/10/05

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
2202 North West Shore Boulevard #450 Tampa, Florida 33607	(813) 288-0040

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

C

4 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Office of Drug Safety

MEMO

To: Russell Katz, M.D.
Director, Division of Neurology Products
HFD-120

From: Felicia Duffy, RN
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Alina R. Mahmud, RPh, M.S., Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Date: September 14, 2005

Re: ODS Consult 00-0159-4, Emsam (Selegiline Transdermal System)
20 mg; NDA 21-336
20 mg; 30 mg, 40 mg; NDA 21-708

This memorandum is in response to an August 26, 2005 request from your Division for a re-review of the proprietary name, Emsam (NDA's 21-336 and 21-708). NDA 21-708 was administratively created to address the maintenance treatment of major depressive disorder, with the acute treatment indication retained under the existing NDA 21-336. The proposed proprietary name was found acceptable by DMETS on September 13, 2000 (ODS consult # 00-0159), January 17, 2002 (ODS consult # 00-0159-1), October 29, 2003 (ODS consult # 00-0159-2), and June 20, 2005 (ODS consult #00-0159-3).

Since the completion of our last consult, DMETS has identified one additional proprietary name , as having look-alike similarities to Emsam.

. Based on these product differences and the lack of convincing look-alike properties, the potential for name confusion between Emsam and [redacted] is minimal.

In summary, DMETS has no objections to the name Emsam from a safety perspective. Additionally, DDMAC has no objections to the name from a promotional perspective. Revised labels and labeling were not submitted for review. Therefore, reference is made to ODS consult 00-0159-2, dated October 29, 2003, which provides recommendations for the labels and labeling of Emsam. We consider this a final review. However, if the approval of the NDA's are delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before the NDA approvals will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

If you have any questions or need clarification, please contact DMETS Project Manager, Diane Smith, at 301-796-0538.

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/s/

Felicia Duffy
9/30/2005 01:08:58 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
9/30/2005 01:11:32 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
9/30/2005 01:24:38 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: October 4, 2005

TO: Thomas Laughren, M.D., Director
Division of Psychiatric Products

VIA: Doris Bates, Ph.D., Regulatory Project Manager
Division of Psychiatric Products

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support

THROUGH: Gerald Dal Pan, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support

SUBJECT: DSRCS Review #2 of Patient Labeling for Emsam (selegiline transdermal system), NDAs 21-336 and 21-708

The sponsor submitted a complete response on May 26, 2005, to the January 30, 2004, Approvable Letter for Emsam, NDAs 21-336 and 21708. Labeling was also revised to reflect the now required Boxed Warning and Class Antidepressant Medication Guide (About Using Antidepressants in Children or Teenagers).

The Patient Information Subcommittee (PISC) met on June 19, 2005, and part of the discussion included products (such as Emsam) that are required to have a Class Medication Guide (MG), but also have a need to include product specific patient information. The PISC decided that:

1. **Products that are required to have a MG cannot also have a separate patient information leaflet. The MG would be the only allowable patient labeling.**

2. **A required Class MG may be expanded to include product-specific information.**

We recommend that the sponsor revise and expand the required Class MG to include Emsam-specific information, since there is important patient information about EMSAM that is not included in the Class MG.

We will be happy to review a revised Medication Guide for Emsam. Please call us if you have any questions.

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

/s/

Jeanine Best
10/4/2005 03:32:26 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
10/5/2005 08:16:40 AM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040
August 31, 2005

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Thomas Laughren, M.D.
Acting Director, Division of Psychopharmacological
Drug Products (HFD-130)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA # 21,336/21,708- N: 058/006
NDA # 20,647/19,334- N: 022/027
EMSAM® (Selegiline Transdermal System)/Eldepryl® (Selegiline Hydrochloride)
Requested Melanoma Data –DATATOP
Information Document: Selegiline Exposure with Concomitant Oral Contraceptive/
Hormone Replacement Use

Dear Sirs:

Reference is made to the Agency's June 15, 2005 request for melanoma information and to subsequent teleconferences with the Division and with Dr. Laughren, respectively.

In an effort to help facilitate the Division's discussions on September 7, 2005, provided within this document are the following data/information:

- DATATOP Data Sets as requested on the August 1, 2005 teleconference regarding the Division's request for information on melanoma and selegiline.
- A background document describing results of epidemiologic, pharmacovigilance and published literature searches around the issue of melanoma with anti-Parkinson's drugs.
- A background document providing data from our NDA and published literature on the concomitant use of selegiline and oral contraceptives/hormone replacement therapies.

Desk copies of this document have been provided to Dr. Doris Bates and Dr. Greg Dubitsky.

If you should require any further information regarding this submission, I can be reached at (813) 288-0040, extension 276.

Sincerely,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc, RAC
Group Director, Regulatory Affairs/Quality Assurance

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: ODS/DMETS HFD-420			FROM: HFD-120 / Dr. D. Bates for Dr. G. Dubitsky	
DATE 8/26/05	IND NO. (46,944)	NDA NO. **21-336 & 21-708**	TYPE OF DOCUMENT Trademark re-review request	DATE OF DOCUMENT NDA resubmission rec'd 5/27/05
NAME OF DRUG EMSAM (transdermal selegiline)	PRIORITY CONSIDERATION Class 1 2-month review		CLASSIFICATION OF DRUG antidepressant	DESIRED COMPLETION DATE: Action due 11/25/05 (see below)

NAME OF FIRM: Somerset Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a resubmission of the trademark EMSAM for consideration, given that the NDA action due date has been changed to six months – therefore the present review is now dated more than 90 days from the likely action date (11/27/05, but last business day is 11/25)

A copy of the most recent review, and of the consult form for it, is attached for your convenience.

Thank you, and please feel free to contact the project manager at 3012-594-5536 or by email at batesd with any questions.

SIGNATURE OF REQUESTER *Doris J. Bates, Ph.D.*	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

August 16, 2005

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Thomas Laughren, M.D.
Acting Director
Division of Psychiatric Drug Products (HFD-130)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA # 20,647/19,334- N:021/026
NDA 21,336/21,708- N:057/005
ELDEPRYL® (Selegiline Hydrochloride) Capsules/Tablets
EMSAM® (Selegiline Transdermal System)
June 15, 2005 Request for Melanoma Data

Dear Sirs:

Reference is made to the Agency's June 15, 2005 request for melanoma data for selegiline clinical trials across all indications and dosage forms, both oral and transdermal. Further reference is made to Somerset's August 1, 2005 teleconference with the Agency.

As requested in the June 15, 2005 letter and further described in the August 1, 2005 teleconference, enclosed please find a CD containing SAS Transport files for Somerset's controlled and extension clinical trials for EMSAM and the controlled data set for Eldepryl (Deprenyl). In addition, the requested demographics table for both selegiline and EMSAM is also included, as a WORD file, on this CD.

Further, as requested by Dr. Greg Dubitsky during a telephone conversation with Somerset on August 15, 2005, enclosed please find a revised Table 2 from Somerset's July 25, 2005 submission regarding the requested melanoma data. This Table now represents the revised exposure Ns as discussed during our call.

If you should have any questions or require any further information, please do not hesitate to contact me at (813) 288-0040.

Very Truly Yours,

Melissa L. Goodhead

Melissa L. Goodhead, B.S., RAC
Group Director
Regulatory Affairs and Quality Assurance

MEMORANDUM OF TELEPHONE CALL

Date: August 15, 2005
NDA: 21-336
Subject: July 21, 2005 submission RE: melanoma
Firm: Somerset
Drug: EMSAM (selegiline transdermal system)
POC: Melissa Goodhead
Phone #: 813-288-0040 ext. 276

I had contacted Ms. Goodhead on August 12, 2005, regarding the above submission. At that time, I conveyed my concern that the number of patients exposed to selegiline transdermal system (STS) to date in Phase 2/3 trials did not appear to be correct (N=2,467) since exposure was over 2,700 patients in these trials in 2003. She was unable to provide a satisfactory explanation. Thus, I requested to speak with the author of the information contained in this submission to obtain clarification.

Ms. Goodhead arranged a telephone conference between Drs. Mel Sharoky and Larry Blob and me. Dr. Blob indicated that indeed there was an error in the number of patients exposed to STS. The correct number is 3,365. Also, he noted that the number of patients exposed only to placebo in Phase 2/3 trials was 695, not 1,240, and the patient-days of exposure were correct as indicated in that submission.

I requested a corrected submission for our records and Dr. Sharoky agreed to forward one to us. I thanked them for their help and the call was terminated.

Gregory M. Dubitsky, M.D.
August 15, 2005

cc: NDA #21-336
HFD-120
HFD-120/GDubitsky
/TLaughren
/PAndreason
/JRacoosin
/MJones
/DBates

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/s/

Greg Dubitsky
8/15/2005 04:44:33 PM
MEDICAL OFFICER

MEMORANDUM OF TELEPHONE CALL

Date: August 12, 2005
NDA: 21-336
Subject: July 21, 2005 submission RE: melanoma
Firm: Somerset
Drug: EMSAM (selegiline transdermal system)
POC: Melissa Goodhead
Phone #: 813-288-0040 ext. 276

Somerset provided this submission in response to our June 15, 2005, request for data regarding melanoma in selegiline clinical trials. During the course of reviewing this submission, I discovered a discrepancy between the number of patients exposed to EMSAM in Phase 2/3 trials reported in Table 1 of this document (2,467) and the number reported in the ISS Amendment in the sponsor's previous submission, dated July 31, 2003 (2,740). Since the EMSAM clinical trials have accrued additional patients since 2003, it is unclear to me how the current number could be about 300 patients less than the previous number.

I contacted Somerset by telephone and Ms. Goodhead was asked to explain this discrepancy and to indicate if there were patients in the Phase 2/3 studies that were excluded from their search for cases of melanoma. She indicated that she would research my question and respond by Email. I told her that this would be satisfactory and thanked her in advance. The telephone call was terminated.

Gregory M. Dubitsky, M.D.
Medical Officer
August 12, 2005

cc: NDA #21-336
HFD-120
HFD-120/GDubitsky
/TLaughren
/PAndreason
/DBates

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/s/

Greg Dubitsky
8/12/05 03:31:06 PM
MEDICAL OFFICER

Meeting Minutes, Teleconference
NDA 21-336, NDA 21-708
EMSAM® (selegiline transdermal system) (Somerset Pharmaceuticals)
NDA 19-334, 20-647
Eldepryl (selegiline) Tablets and Capsules

Date/Time/Place: 1 August 2005, 10:00 a.m., WOC II 4029
Participants: *FDA:* DPP: T. Laughren, P. Andreason, G. Dubitsky, D. Bates
DNP: R. Katz, J. Feeney, J. Racoosin, L. Kapcala, L. Jones, T. Wheelous
ONDC: D. Klein
Somerset: M. Sharoky, L. Blob, A. Azzaro, G. Moonsammy, C. VanDenBerg, M. Goodhead

Background:

- NDAs 21-336 and 21-708, for transdermal selegiline in the treatment of depression, were received May 24, 2001 and July 31, 2003. 21-336 has received two prior actions, Not Approvable on March 25, 2002 and Approvable on January 30, 2004. NDA 21-708 also received an Approvable action on January 30, 2004.
- Both NDAs received a Class 2 Complete Response on May 26, 2005.
- During initial evaluation of these responses DPP became aware of the possible association of anti-Parkinson's disease therapies with malignant melanoma, an issue that has been under exploration in DNP.
- A letter was sent to Somerset on June 15, 2005 requesting melanoma data for selegiline clinical trials across all indications and dosage forms, both oral and transdermal.
- Following this letter, a teleconference was scheduled for Somerset with both Divisions, to further discuss and clarify the issue.
- Somerset responded to the FDA letter on July 21, with a preliminary analysis of data.

Discussion:

- **EMSAM:** Somerset explained that they had reviewed the clinical trials data for the patch and identified no cases of malignant melanoma. Seven different clinical trials databases were reviewed, including not only depression and Parkinson's studies, but also Alzheimer's disease, [redacted], cocaine addiction, and HIV-associated dementia.
- The Divisions requested that these data be presented in the database format described in the June 15 letter, to facilitate meta-analysis if needed.
- The Divisions agreed that only the clinical trials data would be needed in SAS .xpt format, excluding the variables associated with observed melanoma cases such as time of initial diagnoses, etc. These would be the controlled trial files (page 4 of letter) and the extension trial files (pages 5-7 of letter)
- The safety review team (DNP) will provide a WORD formatted table which can be populated by Somerset to provide the needed demographic data, rather than requiring the patient database files as described in the June 15 letter.

- **ELDEPRYL:** DNP needs the data for these clinical trials as well.
- The NDA is ca. 20 years old, n = ca. 100 patients, and the files are not available in electronic format. Somerset will review the relevant CRFs and extract the needed data, compiled as described above.

- Somerset was also requested to seek access to the data from the DATATOP study, and, if possible, review, format and submit it similarly.

- **IMPACT ON PENDING NDAs:** Somerset expressed concern about the impact of this issue on the pending NDAs for EMSAM.
- FDA explained that concerns related to this issue have evolved over time.
  - Since the MDD population is younger than the Parkinson's population, and chronically ill, their exposure may be significantly greater.
  - DPP indicated that this issue may possibly be included on the agenda for a tentative fall Psychopharmacological Drugs Advisory Committee meeting. Somerset will be kept closely informed.

The teleconference concluded cordially. The requested WORD file (demographic data table to fill in) was sent to Somerset by secure electronic mail on August 4, 2005.

[see electronic signature page]

Doris J. Bates, PhD, RPM
Regulatory Project Manager
Division of Psychiatry Products

Thomas P. Laughren, MD
Acting Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doris Bates
8/9/05 03:46:56 PM
CSO

Thomas Laughren
8/9/05 04:11:35 PM
MEDICAL OFFICER

D

1 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
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(813) 288-0040

July 21, 2005

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

Thomas Laughren, MD
Acting Division Director
Division of Psychiatry Products (HFD-130)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852

RE: Request for Information: Malignant Melanoma
NDA 20-647/NDA 19-334: Eldepryl Capsules/Tablets
NDA 21-336/NDA 21-708: Selegiline Transdermal System

Dear Sirs:

Reference is made to the Division's June 15, 2005 request for information to the above stated New Drug Applications. Somerset has reviewed your request and has conducted a review of the available databases for our clinical programs. As such, we offer the following.

I. NDA 19-334/20-647: Eldepryl® (selegiline hydrochloride) Tablets/Capsules 5 mg.

Reference is made to Somerset's November 18, 2003 response to the Division's October 11, 2003 request for information. As described within this response, Somerset's NDA 19-334 for Eldepryl® Tablets was approved under orphan drug status, in 1989, and as such, a database does not exist to allow Somerset to conduct a search for potential adverse events of melanoma. In addition, NDA 20-647 for Eldepryl® Capsules was a reference application with bioequivalence data only and therefore the requested databases are not applicable. A copy of Somerset's November 18, 2003 letter to Ms. Teresa Wheelous is provided in Tab I of this document.

Somerset has also reviewed a copy of the Agency's post-marketing selegiline hydrochloride tablet and capsule safety database, for the years through 2004, and have identified only one reported case of melanoma (FDA Case #3323581), submitted by DuPont Pharmaceuticals in 1999.

We believe this information satisfies the Division's request as it relates to NDAs 20-647 and 19-334.

II. NDA 21-336/21-708: Selegiline Transdermal System

Somerset conducted an evaluation of its Phase II and III clinical databases relating to the selegiline transdermal system across all indications studied. This database evaluation was conducted in a two-tier fashion by a physician monitor. The first review (level-1 review) consisted of a computer-generated listing of patient data identified by adverse event search terms. Based on a specific algorithm, patients were then selected for comprehensive medical review (levl-2 review) by the physician monitor. This review failed to reveal any cases of newly diagnosed melanoma within Somerset's clinical trial databases. An overview, methodology and results summary of this evaluation is provided in Tab 2 of this document.

Somerset believes it has now satisfied the Division's request as it relates to NDA 21-336 and NDA 21-708.

Should you have any questions or require any further information, please do not hesitate to contact me at (813) 288-0040, extension 276.

Very Truly Yours,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc., RAC
Group Director, Regulatory Affairs/Quality Assurance

:mlg

Desk Copies: Dr. Doris Bates (12 copies)

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

June 21, 2005

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA # 21,336/21,708
EMSAM® (Selegiline Transdermal System)
CMC: Drug Substance Assignment to Finished Product Lots
N: 052

Dear Dr. Katz:

As requested by Dr. Donald Klein, enclosed please find a table representing drug substance lot assignment to drug product lot submitted within the June 9, 2005 stability update. In addition, copies of the corresponding certificates of analysis for each drug substance lots are provided.

If you should require any further information regarding this submission, I can be reached at (813) 288-0040, extension 276.

Sincerely,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc., RAC
Group Director, Regulatory Affairs/Quality Assurance

:mlg

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

July 18, 2005

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA No. 21-336/21,708
EMSAM® (SELEGILINE TRANSDERMAL SYSTEM)
REQUESTED CMC INFORMATION
N: 053

Dear Dr. Katz:

Pursuant to 21 CFR 314.50(d)(1)(ii)(c) and at the request of Dr. Donald Klein, enclosed please find the following documents:

- Manufacturing Flow Diagram for the Selegiline Transdermal System (STS)
- Listing of Equipment used during the manufacturing of the STS Validation Lots
- Batch Production Records for and finished product for EMSAM® 20mg/20cm^2
- Packaging Control Sheet for EMSAM® 20mg/20cm^2

In addition, at the request of Dr. Klein, I am enclosing a copy of the Certificate of Analysis (COA) for each of the EMSAM® validation lots.

This information has also been provided, via desk copy, to Dr. Klein.

If you should have any questions or require any further information, please do not hesitate to contact me at (813) 288-0040, extension 276.

Very Truly Yours,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc., RAC
Group Director of Regulatory Affairs/Quality Assurance

:mlg

Office of Drug Safety

MEMO

To: Russell Katz, M.D.
Director, Division of Neuropharmacological Drug Products
HFD-120

From: Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Alina R. Mahmud, R.Ph., M.S., Team Leader
Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

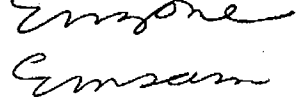
Date: June 20, 2005

Re: ODS Consult 00-0159-3, Emsam (Selegiline Transdermal System)
20 mg; NDA 21-336
20 mg; 30 mg, 40 mg; NDA 21-708

This memorandum is in response to a May 27, 2005 request from your Division for a re-review of the proprietary name, Emsam (NDAs 21-336 and 21-708). NDA 21-708 was administratively created to address the maintenance treatment of major depressive disorder, with the acute treatment indication retained under the existing NDA 21-336. The proposed proprietary name was found acceptable by DMETS on September 13, 2000 (ODS Consult # 00-0159), January 17, 2002 (ODS Consult # 00-0159-1), and October 29, 2003 (ODS Consult # 00-0159-2).

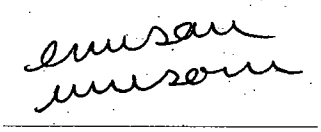
Since the completion of our last consult, DMETS has identified three additional proprietary names, Enzone, Unisom, and Imuran, having look-alike and/or sound-alike similarities to Emsam.

1. Enzone may look like Emsam when scripted. Enzone is hydrocortisone and pramoxine cream, 1%/1%, indicated for use in acute dermatologic conditions where anti-inflammatory and topical anesthetic properties are required. Patients should not use Enzone for longer than 14 days without consulting with their doctor. Enzone and Emsam owe look-alike properties to similarities in the "En" vs. "Em" beginning and "on" vs. "am" ending. However, the downstroke of the letter "z" in Enzone when scripted in cursive writing may serve to differentiate the names orthographically, (see sample below).



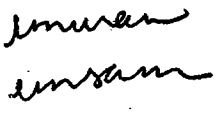
Despite some orthographic similarities, Enzone and Emsam have product differences including, dosage form (cream vs. transdermal patch), strength (1%/1% vs. 20 mg, 30 mg, and 40 mg), dosing regimen (apply two to four times daily vs. once daily application), and duration of use (short-term use vs. chronic use), respectively. Based on these product differences and lack of convincing look-alike properties, the potential for name confusion between Enzone and Emsam is minimal.

2. Unisom may look like Emsam when scripted. Unisom is Doxylamine Succinate Tablets, an over-the-counter (OTC) sleep aid. Unisom and Emsam owe look-alike properties to similarities in the series of short up and down strokes that begin each name, "uni" vs. "em", and virtually identical endings "som" vs. "sam" when scripted in cursive lower case writing (see sample below).



In addition to look-alike similarities of Unisom and Emsam, both products are to be administered once a day. Unisom and Emsam have product differences including, route of administration (oral vs. topical), dosage form (tablet vs. transdermal patch), strength (25 mg vs. 20 mg, 30 mg, and 40 mg), prescriptive status (OTC vs. prescription only), and duration of use (prn use vs. chronic use), respectively. Because Emsam is available in multiple strengths, a strength must be included on prescriptions. Based on these product differences, the potential for name confusion between Unisom and Emsam is minimal.

3. Imuran may look like Emsam when scripted. Imuran is azathioprine tablets, indicated for renal homotransplantation and rheumatoid arthritis. Imuran and Emsam owe look-like similarities to the shared letters, "m" and "a", as well as letters which look alike when scripted in cursive, "i" vs. "e", "r" vs. "s", and terminal "n" vs. "m" (see sample below).



In addition to look-alike similarities of Imuran and Emsam, both products are to be administered once a day. Although there are orthographic similarities in the names, Imuran and Emsam have product differences including, route of administration (oral vs. topical), dosage form (tablet vs. transdermal patch), and strength (50 mg vs. 20 mg, 30 mg, and 40 mg), respectively. Because Emsam is available in multiple strengths, a strength must be included on prescriptions. Based on the product differences, the potential for name confusion between Imuran and Emsam is minimal.

In summary, DMETS has no objections to the name Emsam from a safety perspective. Additionally, DDMAC has no objections to the name from a promotional perspective. Reference is made to ODS Consult 00-0159-2, dated October 29, 2003, which provides recommendations for the labels and labeling of these products. We consider this a final review. However, if the approval of the NDA's are delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before the NDA approvals will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

If you have any questions or need clarification, please contact DMETS Project Manager, Diane Smith, at 301-827-1998.

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

/s/

Charles Hoppes
7/15/05 11:16:06 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
7/15/05 11:46:05 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/15/05 12:06:00 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-336
NDA 21-708
NDA 20-647
NDA 19-334

Somerset Pharmaceuticals, Inc.
Attention: Melissa L. Goodhead
Group Director of Regulatory Affairs / Quality Assurance
2202 N. West Shore Boulevard, Suite 450
Tampa, Florida 33607

Dear Ms. Goodhead:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMSAM (selegiline transdermal system) [NDA 21-336, submitted on May 4, 2001, and NDA 21-708, submitted on October 15, 2003.]

We also refer to your submissions to both above referenced new drug applications, dated May 26, 2005. These submissions have been accepted as complete Class 2 responses to our January 30, 2004 action letter.

We are reviewing the clinical sections of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDAs.

MALIGNANT MELANOMA

The Division of Neuropharmacological Drug Products has been investigating a possible association of anti-Parkinson's disease therapies with malignant melanoma. In this connection, specific information related to the use of selegiline capsules and tablets (under the trademark ELDEPRYL, NDAs 20-647 and 19-334) has previously been requested from your firm (letter, November 7, 2001; letter, October 11, 2003; telefax, November 17, 2003).

In considering selegiline as a transdermally applied therapy for the treatment of major depressive disorder (MDD), we have become aware that the potential association of selegiline treatment with melanoma should also be considered in this indication.

The MDD patient population is considerably younger than the population of Parkinson's disease patients, and could potentially be treated for a significantly longer time. In addition, we know that transdermal dosing of selegiline results in substantially higher exposure to selegiline parent drug and lower exposure to its metabolites compared to oral dosing, where extensive first-pass metabolism occurs. Furthermore, the transdermal route of delivery may itself elevate the risk of melanoma at the patch application site. We cannot predict the effect of these three factors on the potential for development or promotion of melanoma in the MDD patient population, but it seems plausible that any of these alone could increase the risk of melanoma with transdermal selegiline compared to oral selegiline (if such a risk exists).

We note also that neither the carcinogenicity nor the chronic local toxicity of transdermal selegiline has, as yet, been assessed. Although the Division has previously agreed that this could be done in the context of Phase 4 studies (2-year transdermal mouse carcinogenicity study), the lack of these data at present increases the difficulty of risk assessment with regard to cancer risk.

We have therefore decided to request data on melanoma cases and person-time exposure for all selegiline products, both oral and transdermal. We are requesting that you submit the datasets described, submitted as SAS transport files (x-port engine). The data request, detailed in the attachment following this letter, asks that you review the data from all clinical trials of selegiline in all indications and formulations studied, and submit the number of melanoma cases and the person-time exposure data from both randomized controlled trials and open label trials. To facilitate our use of these data across indications, please construct the datasets using the variable names and architecture as described in the attachments.

Please also provide a list of trials by indication, formulation, number, and title of each trial. If it is not clear from the title of the study, please indicate whether selegiline was used as an adjunctive treatment or as monotherapy. Please include a glossary of all abbreviations used. Importantly, for each trial, please provide a description and the timing of any specific assessments to detect the emergence of skin lesions. This should include not only an examination of the transdermal patch application sites for the trials that used this formulation, but also any comprehensive total body skin examinations that were conducted in any trials. This information is critical in allowing an evaluation of the sensitivity of these trials in detecting melanoma.

Please also submit a narrative summary describing each case of melanoma identified during the development programs for all dosage forms of selegiline. Be as specific as possible regarding the stage of the melanoma at diagnosis and whether the lesion was present prior to initiation of the trial (e.g., at screening). Please include all pathology reports available. If at all possible, the tumor should be described as either invasive or local.

The requested information should be submitted ***en bloc*** to all four NDAs referenced, but may be submitted to NDA 21-336 for the transdermal patch with cross-reference to NDA 21-708. Submissions should also be made to both NDA 20-647 (capsules) and NDA 19-334 (tablets); again, one of these submissions may be made via cross-reference. Because we anticipate creation of separate neurology and psychiatry Divisions from the present Division of Neuropharmacological Drug Products within the six month review time frame for the pending psychiatric NDAs, please assure that separate submissions are made to both the oral and transdermal NDAs, to facilitate future access by reviewers in both Divisions.

We will be happy to discuss the details of this request with you. If you have any questions with regard to the psychiatric indications, please contact Doris J. Bates, Ph.D., Regulatory Project Manager, by telephone at (301) 594-2850 or via secure e-mail at batesd@cder.fda.gov . For specific questions on the neurologic indications, please contact Teresa Wheelous, Regulatory Management Officer, at the same number listed above.

Sincerely,

{*See appended electronic signature page*}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT 1: DESCRIPTION OF DATASETS AND VARIABLE NAMES

CONTROLLED TRIAL FILE - this file should contain trial design and overall enrollment information about each controlled trial, leading to one row per trial. Please provide the variables in the same order as shown below.

- **(TRIAL)** – trial identifier;
- **(IND)** – indication being studied;
- **(FORM)** – formulation studied [CODE: 1 = oral; 2 = transdermal]
- **(LOC)** – geographic locations of study centers;

[CODE: 1=North American centers only (e.g., US/Canada); 2=Non-North American centers only; 3=both North American and Non-North American Centers]

- **(TYEAR)** – calendar year trial was **initiated**;
- **(CTRL)** – describes type of trial control used;

[CODE: P= placebo-controlled; A=active-controlled; PA= placebo- and active-controlled]

- **(DUR)** – duration of trial in weeks
- **(SET)** – setting trial population drawn from;

[CODE: I= inpatient; O=outpatient; IO=inpatient and outpatient]

- **(TXRI)** – name of run-in treatment (drug name or placebo); NA if trial design did not include a run-in phase;
- **(TXI)** – name of post-randomization investigational treatment (drug name);
- **(TXAC)** – name of post-randomization active control treatment (drug name); NA if trial design did not include an active control;
- **(LEVOADJ)** – investigational treatment is being studied as an adjunct to levodopa (i.e., all enrolled patients are taking levodopa concomitantly with study drug);

[CODE: Y =yes, N=no, U= unknown]

- **(RI)** – number of patients entering run-in phase; NA if trial design did not include a run-in phase;
- **(RIE)** – number of patients who **actually received** at least one dose of **run-in** treatment; NA if design did not include a run-in phase;
- **(RANI)** – number of patients randomized to **investigational** treatment;
- **(RANPC)** – number of patients randomized to **placebo control**; NA if trial design did not include a placebo control;
- **(RANAC)** – number of patients randomized to **active control**; NA if trial design did not include active control;
- **(RANEI)** – number of patients who **actually received** at least one dose of post-randomization **investigational** treatment;
- **(RANEPC)** – number of patients who **actually received** at least one dose of post-randomization **placebo** control; NA if trial design did not include a placebo control;
- **(RANEAC)** – number of patients who **actually received** at least one dose of post-randomization **active** control; NA if trial design did not include an active control;
- **(MRI)** – number of melanomas diagnosed **during run-in phase**; NA if trial design did not include a run-in phase;
- **(MI)** – number of post-randomization melanomas diagnosed in patients **on investigational treatment;**

- **(MPC)** – number of post-randomization melanomas diagnosed in patients **on placebo control;** NA if trial design did not include a placebo control;
- **(MAC)** – number of post-randomization melanomas diagnosed in patients **on active control;** NA if trial design did not include an active control;

EXTENSION TRIAL FILE - this file should contain trial design and overall enrollment information about each extension trial, leading to one row per trial. Please provide the variables in the same order as shown below.

- **(TRIAL)** – trial identifier;
- **(IND)** – indication being studied;
- **(FORM)** – formulation studied [CODE: 1 = oral; 2 = transdermal]
- **(LOC)** – geographic locations of study centers;

[CODE: 1=North American centers only (e.g., US/Canada); 2=Non-North American centers only; 3=both North American and Non-North American Centers]

- **(TYEAR)** – calendar year trial was **initiated**;
- **(CTRL)** – describes type of trial control used;

[CODE: A= active-controlled; O= open]

- **(DUR)** – duration of trial in weeks
- **(SET)** – setting trial population drawn from;

[CODE: I= inpatient; O= outpatient; IO= inpatient and outpatient]

- **(TXI)** – name of extension investigational treatment (drug name);
- **(TXAC)** – name of extension active control (drug name); NA if trial design did not include an active control;
- **(EXTI)** – number of patients enrolled in **investigational** treatment;
- **(EXTAC)** – number of patients enrolled in **active control**; NA if trial design did not include active control;
- **(EXTEI)** – number of patients who **actually received** at least one dose of extension **investigational** treatment;
- **(EXTEAC)** – number of patients who **actually received** at least one dose of extension **active** control; NA if trial design did not include an active control;
- **(MI)** – number of melanomas diagnosed in patients **on investigational treatment;**
- **(MAC)** – number of melanomas diagnosed **on active control;** NA if trial design did not include an active control;

Controlled trials -PATIENT FILE: this file should contain the following variables for each patient participating in a controlled trial, leading to one row per patient. Please provide the variables in the same order as shown below.

- **(TRIAL)** – trial identifier;
- **(IND)** – indication being studied;
- **(FORM)** – formulation studied [CODE: 1 = oral; 2 = transdermal]
- **(CTPID)** – controlled trial patient identifier;
- **(AGE)** – patient age in years [U= unknown];
- **(GEN)** – patient gender [CODE: M= male; F=female; U= unknown];
- **(RACE)**- patient race [CODE: W= White; B= Black; A= Asian; O= Other];

- **(LEVOYRS)**- duration of prior levodopa therapy in years; enter 0 if none;
- **(LEVO)** – patient was taking levodopa concomitantly with the study drug

[CODE: Y= yes; N=no, U= unknown];

- **(DAAYRS)** – duration of prior dopamine agonist therapy in years; enter 0 if none
- **(DAA)** – patient was taking a dopamine agonist concomitantly with the study drug [CODE: Y = yes; N = no]
- **(DAANAME)** – name of dopamine agonist taken by patient
- **(RITX)** – **run-in treatment** for this patient (drug name or placebo); NA if trial design did not include a run-in phase;
- **(FDRI)** – date of **first dose of run-in** treatment; NA if trial design did not include a run-in phase;
- **(LDRI)** – date of **last dose of run-in** treatment; NA if trial design did not include a run-in phase;
- **(RANTX)** – **randomized treatment** for this patient (name of investigational treatment, placebo, or name of active control treatment; NA if patient discontinued or died during run-in);
- **(FDRAN)** – date of **first dose of randomized** treatment;
- **(LDRAN)** – date of **last dose of randomized** treatment;
- **(RESCUE)** – patient started levodopa **during** study as a "rescue" medication

[CODE: Y= yes; N= no, U= unknown];

- **(FDRESC)** -date of **first dose of rescue** treatment; NA if patient did not require rescue medication;
- **(RIDX)** – patient diagnosed with melanoma during **run-in phase**

[CODE: Y= yes; N= no];

- **(RANDX)** – patient diagnosed with melanoma **after randomization**

[CODE: Y= yes; N=no; RI=patient diagnosed during run-in];

- **(DDATE)** – date of diagnosis of melanoma

[Enter the date; U= unknown; NA= patient did not have melanoma];

- **(DD30)** – melanoma diagnosed within 30 days of last dose of study treatment

[CODE: Y= yes; N=no; U=unknown; NA= patient did not have melanoma]

Extension trials- PATIENT FILE: this file should contain the following variables for each patient participating in an extension trial, leading to one row per patient. Please provide the variables in the same order as shown below.

- **(TRIAL)** – trial identifier;
- **(IND)** – indication being studied;
- **(FORM)** – formulation studied [CODE: 1 = oral; 2 = transdermal]
- **(CTPID)** – controlled trial patient identifier;
- **(EXTPID)** – extension trial patient identifier (if different from CTPID);
- **(AGE)** – patient age in years [U= unknown];
- **(GEN)** – patient gender [CODE: M= male; F= female; U= unknown];
- **(RACE)**- patient race [CODE: W= White; B= Black; A= Asian; O= Other];
- **(RANTX)** – **randomized treatment** for this patient (name of investigational treatment, placebo, or name of active control treatment);
- **(EXTTX)** – **extension treatment** for this patient

- **(LEVO)** – patient was taking levodopa concomitantly with the extension treatment
[CODE: Y= yes; N= no, U= unknown];
- **(DAA)** – patient was taking a dopamine agonist concomitantly with the extension treatment [CODE: Y = yes; N = no]
- **(DAANAME)** – name of dopamine agonist taken by patient
- **(FDEX)** – date of **first dose of extension** treatment;
- **(LDEX)** – date of **last dose of extension** treatment;
- **(RESCUE)** – patient started levodopa **during** study as a "rescue" medication
[CODE: Y =yes; N= no, U= unknown];
- **(FDRESC)** -date of **first dose of rescue** treatment; NA if patient did not require rescue medication;
- **(EXTDX)** – patient was diagnosed with melanoma during **extension**
[CODE: Y =yes; N= no; RCT= patient diagnosed during controlled trial];
- **(DDATE)** – date of diagnosis of melanoma
[Enter the date; U= unknown; NA= patient did not have melanoma];
- **(DD30)** – melanoma diagnosed within 30 days of last dose of study treatment
[CODE: Y =yes; N= no; U= unknown; NA= patient did not have melanoma]

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
6/15/05 02:38:48 PM

Minutes of Meeting
NDA 21-336, NDA 21-708: EMSAM® (Selegiline Transdermal System)
Somerset Pharmaceuticals, Inc.: Major Depressive Disorder
(Acute and Long-Term Treatment)
Resubmission Filing Meeting Minutes

Meeting Date / Time / Place: June 6, 2005; 10:00 A.M.; DNDP 4th Floor WOC II CR
Input Received From: R. Katz, T. Laughren, G. Dubitsky, R. Baweja, R. Kavanagh, L. Freed, P. Roney, T. Oliver, D. Klein, D. Bates, J. Racoosin (Eldepryl melanoma history, via telecon)

Background: NDA 21-336 was submitted on May 24, 2001 and was the subject of a Not Approvable action on March 25, 2002. A resubmission, including NDA 21-708 for longer-term treatment of depression, was submitted on July 31, 2003. Both NDAs received an Approvable letter on January 30, 2004. A second resubmission to both NDAs was submitted on May 26, 2005.

This resubmission was primarily in paper-only format. However, because of its limited size and the provision of desk copies by the applicant, it was possible for review team members to assess its completeness within the fourteen day interval stipulated by the MaPP.

Meeting Summary:

- The resubmission was agreed to be a **Class 2, 6-month response with an action due date of November 27, 2005.** The effective action date is therefore Friday, November 25, 2005, which is the Friday immediately following Thanksgiving.
- Consults were forwarded for labeling (general) and trademark review.
- A Biopharm consult was forwarded.
- Disciplines reviewing the resubmissions are CMC, Pharm/Tox, OCPB, and Clinical, as well as ODS/DMETS and DSRCS for the tradename and labeling/MedGuide reviews.
- A CMC PAI inspection will be needed and is the primary reason for the six month clock.
- We have set aside time for an Advisory Committee meeting for these NDAs.
- Reviews are due to be completed by late August in order for the Advisory Committee meeting to occur in a timely manner. This would potentially need to include reviews of any new data submitted with regard to melanoma risk (see below).
- **Melanoma.** The issue of potentially increased risk of melanoma was raised during this meeting. Exploration of this potential risk has been underway for several Parkinson's disease drugs including rasagiline (Teva Pharmaceuticals, for which several cases were reported: NDA still pending) and the oral form of selegiline, Eldepryl (Somerset: information request letters were sent in 2001 and 2003; no reply to date). The review team, upon being made aware of the issue, agreed that a similar query should be made ASAP for the transdermal patch, particularly given the

significantly higher bioavailability of parent selegiline via the transdermal route as well as the route of delivery (direct application to the skin).

Post Meeting Notes:

- Per agreement with Dr. Laughren, Dr. Bates completed and forwarded the required acknowledgement letter for a Class 2 Complete Response. This letter issued on June 8, 2005 and a follow-up copy was sent to the firm via secure e-mail on June 10, 2005.

- Dr. Bates performed a file search on the melanoma issue covering rasagiline and selegiline from April 2001 to the present, distributed this information to Drs. Laughren and Dubitsky, obtained an electronic copy of the 2003 Eldepryl IR letter from Ms. T. Wheelous, reviewed all relevant information, and drafted the melanoma IR letter for EMSAM on June 8, 2005. This letter was edited by Drs. Dubitsky and Racoosin, revised by Dr. Bates, reviewed by Dr. Laughren, and forwarded to Dr. Katz for review and signature on June 13, 2005.

- An Advisory Committee meeting has been tentatively scheduled for October 25-26, 2005. Reviews should therefore definitely be completed by late August, 2005.

Please see electronic signature page

Doris J. Bates, Ph.D.
Regulatory Project Manager

Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drugs Group

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/s/

Doris Bates
6/13/05 04:21:15 PM

Thomas Laughren
6/14/05 07:35:02 AM

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

June 9, 2005

DUPLICATE

RECEIVED
JUN 10 2005
DDR-120 / CDER

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA No. 21-336
EMSAM® (SELEGILINE TRANSDERMAL SYSTEM)
STABILITY UPDATE
N: 050

ORIGINAL AMENDMENT
N(EC)

Dear Dr. Katz:

As per my discussion with Dr. Donald Klein, enclosed please find updated stability tables for Somerset's API, selegiline base, and finished product, EMSAM.

Updated stability is provided for API and finished product, as well as I have included the data from the — time point for the nine finished product validation lots (3 lots each dose).

This information has also been provided, via desk copy, to Dr. Klein.

If you should have any questions or require any further information, please do not hesitate to contact me at (813) 288-0040, extension 276.

Very Truly Yours,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc., RAC
Group Director of Regulatory Affairs/Quality Assurance

:mlg

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

June 8, 2005

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA No. 21-336
EMSAM® (SELEGILINE TRANSDERMAL SYSTEM)
REQUESTED TABLES:SAES/DISCONTINUATIONS DUE TO AES
N: 049

Dear Dr. Katz:

As per my discussion with Dr. Greg Dubitsky, enclosed please find the requested tables with line listings of serious adverse events and discontinuations due to adverse events. This information has also been provided, via facsimile, to Dr. Dubitsky.

If you should have any questions or require any further information, please do not hesitate to contact me at (813) 288-0040, extension 276.

Very Truly Yours,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc., RAC
Group Director of Regulatory Affairs/Quality Assurance

:mlg

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-336
NDA 21-708

Somerset Pharmaceuticals, Inc.
Attention: Melissa L. Goodhead
Group Director of Regulatory Affairs / Quality Assurance
2202 N. West Shore Boulevard, Suite 450
Tampa, Florida 33607

Dear Ms. Goodhead:

We acknowledge receipt on May 27, 2005 of your May 26, 2005 resubmissions to your above referenced new drug applications for EMSAM (selegiline transdermal system).

We consider these to be complete, Class 2 responses to our January 30, 2004 action letter. Therefore, the user fee goal date for these submissions is November 27, 2005.

If you have any questions, please call the undersigned, at (301) 594-2850.

Sincerely,

{See appended electronic signature page}

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doris Bates
6/8/05 01:14:14 PM

Bates, Doris J

From: Bates, Doris J
Sent: Tuesday, June 07, 2005 4:49 PM
To: CDER ODS CONSULTS
Subject: NDA 21-336 & NDA 21-708 DEADLINE CHANGE FROM TWO MONTHS TO SIX MONTHS
Importance: High

The review time frame for these resubmissions has changed from two months to six months. The new deadline for action is November 25, 2005. We have an internal deadline for compilation of all reviews and consults of October 3, 2005.

I will place a copy of this message in DFS as an addendum to the consults sent on 5/31/05 for both NDAs.

This includes the overall labeling consult including MedGuide as well as the trademark consult.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doris Bates
6/7/05 04:50:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: ODS/DMETS HFD-420			FROM: HFD-120 / Dr. D. Bates for Dr. G. Dubitsky	
DATE 5/27/05	IND NO. (46,944)	NDA NO. **21-336 & 21-708**	TYPE OF DOCUMENT trademark re-review request	DATE OF DOCUMENT NDA resubmission rec'd 5/27/05
NAME OF DRUG EMSAM (transdermal selegiline)	PRIORITY CONSIDERATION Class 1 2-month review		CLASSIFICATION OF DRUG antidepressant	DESIRED COMPLETION DATE: Action due 7/27/05 (see below)

NAME OF FIRM: Somerset Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please see attached information. The resubmission is all paper, there are no .pdf files of labeling in the EDR; however, there is a WORD file of the proposed PI. The firm has included full size mockups of the package insert which I will forward as soon as received. NOTE THERE IS NOW A MEDGUIDE AS WELL.

I have attached three copies of the volume containing the relevant labeling in its entirety for DMETS, trademark, and MEDGUIDE review. I will put a duplicate of this consult into DFS as the trademark consult request. I am also including a copy of the FDA's AE letter (January, 2004) with the hard copies of labeling information.

Please feel free to contact the project manager at 4-5536 or by email at batesd with any questions.

SIGNATURE OF REQUESTER *Doris J. Bates, Ph.D.*	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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

/s/

Doris Bates
5/31/05 01:12:15 PM
Assuming two month clock, 120's deadline is July 27, 2005. Consult response needed by early July if at all possible. Includes PPI and MedGuide as well as physician insert and outer labeling.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: ODS/DMETS HFD-420			FROM: HFD-120 / Dr. D. Bates for Dr. G. Dubitsky	
DATE 5/27/05	IND NO. (46,944)	NDA NO. **21-336 & 21-708**	TYPE OF DOCUMENT Trademark re-review request	DATE OF DOCUMENT NDA resubmission rec'd 5/27/05
NAME OF DRUG EMSAM (transdermal selegiline)	PRIORITY CONSIDERATION Class 1 2-month review		CLASSIFICATION OF DRUG antidepressant	DESIRED COMPLETION DATE: Action due 7/27/05 (see below)

NAME OF FIRM: Somerset Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
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- ☐ END OF PHASE II MEETING
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
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- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please see attached information. The resubmission is all paper, there are no .pdf files of labeling in the EDR; however, there is a WORD file of the proposed PI. The firm has included full size mockups of the package insert which I will forward as soon as received.

I have put a duplicate of this consult into DFS as the labeling consult request. I am also including a copy of the FDA's AE letter (January, 2004) with the hard copies of labeling information.

Please feel free to contact the project manager at 4-5536 or by email at batesd with any questions.

SIGNATURE OF REQUESTER *Doris J. Bates, Ph.D.*	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
5/31/05 01:17:27 PM
Labeling consult also sent, labeling includes PPI and MedGuide.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-860: Dr. Baweja, Dr. Kavanagh			FROM: HFD-120: Dr. Bates for Dr. Dubitsky	
DATE May 27, 2005	IND NO. —	NDA NO. 21-336/21-708	TYPE OF DOCUMENT Third Cycle Resubmission	DATE OF DOCUMENT May 27, 2005
NAME OF DRUG EMSAM (selegiline transdermal system)	PRIORITY CONSIDERATION Class I resubmission		CLASSIFICATION OF DRUG depression	DESIRED COMPLETION DATE: July 27, 2005 due date

NAME OF FIRM: Somerset Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☒ BIOAVAILABILTY STUDIES – Labeling comments
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
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- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Submission acceptance meeting on June 6 at 10 a.m. in Div-CR. Copy of FDA's AE letter is included with consult hard copy.

Please notify CSO of any change in reviewer assignments – thanks.

Clinical reviewer remains Dr. Dubitsky, CMC is Dr. Klein.

SIGNATURE OF REQUESTER *Doris J. Bates, Ph.D.*	METHOD OF DELIVERY (Check one) XXX MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
5/31/05 01:32:46 PM
Currently a 2 month clock on the resubmission. Final deadline to be set at the resubmission meeting on June 6.

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

May 26, 2005

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA # 21,336/21,708
EMSAM® (Selegiline Transdermal System)
Formal Response to Approvable Letter/Amendment to NDA
User Fee #4146/4626
N: 048/003

Dear Dr. Katz:

Pursuant to 21 CFR 314.110 and to Somerset's January 31, 2004 Approvable letter, enclosed please find our formal response/amendment to the above referenced NDAs.

For ease of review, we have included a Response Summary individually outlining Somerset's responses to the Division's comments. In addition, all administrative paper work is included in Volume 1 of this submission.

As agreed to by the Division, all case report forms (CRFs) for patients who experienced a serious adverse event (SAE) or withdrew from a study due to a serious or non-serious adverse event, were provided in electronic format to the electronic document room. An electronic copy, in WORD, of the proposed labeling has also been included with the submission to the electronic document room. Desk copies of the requested sections have been provided to the Regulatory Project Manager.

Reference is made to the Pediatric Final Rule (63 FR 66632) and to the Division's March 25, 2002 deferral of the requirement for submission of studies for EMSAM (selegiline transdermal system) under this rule. Somerset is currently evaluating how to proceed in regards to the Pediatric Final Rule and will consult with the Division, at a later date, for further discussion around this.

Pursuant to 21 CFR 314.108, Somerset hereby claims the above stated two NDAs represent a new chemical entity and is entitled to market exclusivity.

Formal reference to this submission is hereby requested and a copy of this cover letter and Form FDA 356h, accompanying this submission, will be filed to NDA 21,708.

If you should require any further information regarding this submission, I can be reached at (813) 288-0040, extension 276.

Sincerely,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc, RAC
Group Director, Regulatory Affairs/Quality Assurance

:mlg

ENVIRONMENTAL ASSESSMENT

May 25, 2005

Reference is made to Dr. Donald Klein's request for information dated September 22, 2003 and to Somerset's September 26, 2003 submission (N:036) to NDA 21, 336 in response to this request. As demonstrated in the revised Claim for Categorical Exclusion, Somerset maintains that this application qualifies for a categorical exemption under 21 CFR § 25.31(b).

Signed: Melissa L. Goodhead Date: 25 May 2005

Melissa L. Goodhead, B.Sc, RAC
Group Director, RA/QA

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

FIELD COPY CERTIFICATION

May 25, 2005

Somerset Pharmaceuticals, Inc. hereby certifies that copies of the required sections of this NDA have been sent to the FDA Field office, Orlando, Florida.

Signed: Melissa L. Goodhead Date: 25 May 2005

Melissa L. Goodhead, B.Sc., RAC
Group Director, RA/QA

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

January 20, 2005

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA No. 21-336/21-708
EMSAM® (SELEGILINE TRANSDERMAL SYSTEM)
TELECONFERENCE/MEETING REQUEST: CMC BRIEFING DOCUMENT- IMPURITIES
N: 047/002

Dear Dr. Katz:

Reference is made to the above stated New Drug Applications (NDAs) and to the Agency's January 30, 2004 Approvable Letter for the referenced NDAs.

As provided for in the Approvable Letter, Somerset hereby requests a teleconference and/or meeting to discuss the Agency's comment regarding specified impurities as described in comment number 2 of the Chemistry, Manufacturing and Controls Section in the letter of January 30, 2004.

In preparation for this teleconference/meeting, Somerset is submitting a briefing document providing additional data and safety information as justification of the proposed impurity specifications for the Selegiline Transdermal System (STS). As part of this preparation, Somerset, with our STS manufacturer —— —— and our CMC/toxicology experts, have conducted a complete evaluation of the impurities currently seen in our finished product. Based on these data and the safety evaluation conducted by our toxicology experts, Somerset believes that the revised specifications are justified and that exposure to the maximum levels of impurities in our STS allowable under these specifications, does not pose a safety risk to patients.

With the addition of this new data and safety information, we are confident this will now satisfy the Agency's concerns with regard to our current impurity specifications for the Selegiline Transdermal System. We are hopeful a meeting and/or teleconference will not be required, however, we are prepared to further discuss this should you feel it necessary.

Somerset is hereby requesting a submission, by reference to NDA 21,708.

If you should have any questions or require any further information, please do not hesitate to contact me at (813) 288-0040, extension 276.

Very Truly Yours,

Melissa L. Goodhead, B.Sc., RAC
Group Director of Regulatory Affairs/Quality Assurance

:mlg

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

January 13, 2005

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA No. 21-336/21-708
EMSAM® (SELEGILINE TRANSDERMAL SYSTEM)
TELECONFERENCE/MEETING REQUEST:
BRIEFING DOCUMENT (N:045)
N: 046

Dear Dr. Katz:

Reference is made to the above stated New Drug Applications (NDAs) and to Somerset's December 21, 2004 submission of a briefing document and request for a meeting.

In the submission dated December 21st, four figures were inadvertently left out of the section contained in Tab II, "Phase IV Commitments". Figures numbered 1-4, referenced on page 91, numbers 1 and 2, are provided herein for inclusion in submission N:045 for the February 9, 2005 teleconference.

If you should have any questions or require any further information, please do not hesitate to contact me at (813) 288-0040, extension 276.

Very Truly Yours,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc., RAC
Group Director of Regulatory Affairs/Quality Assurance

:mlg

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

December 21, 2004

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA No. 21-336/21-708
EMSAM® (SELEGILINE TRANSDERMAL SYSTEM)
TELECONFERENCE/MEETING REQUEST: BRIEFING DOCUMENT
N: 045/001

Dear Dr. Katz:

Reference is made to the above stated New Drug Applications (NDAs) and to the Agency's January 30, 2004 Approvable Letter for the referenced NDAs.

As provided for in the Approvable Letter, Somerset hereby requests a teleconference and/or meeting with the Agency, to discuss EMSAM's labeling and requested Phase IV studies.

In preparation for this teleconference/meeting, Somerset is providing a briefing document which describes Somerset's revised proposed labeling for EMSAM as well as proposals for the requested Phase IV studies.

Somerset is hereby requesting a submission, by reference to NDA 21,708.

If you should have any questions or require any further information, please do not hesitate to contact me at (813) 288-0040, extension 276. I will contact Dr. Doris Bates to initiate scheduling of this teleconference/meeting.

Very Truly Yours,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc., RAC
Group Director of Regulatory Affairs/Quality Assurance

:mlg

Somerset
PHARMACEUTICALS, INC.

202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

November 18, 2003

Ms. Teresa Wheelous
Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA Nos. 19,334/20,647
Requested Information-Melanoma Database

Dear Ms. Wheelous:

Reference is made to our discussion and to the Division's letter dated October 11, 2003 requesting data on melanoma cases of Parkinsonian patients studied within clinical trials for the above referenced NDAs.

Somerset is willing to provide any available information to aid in the Division's construction of a melanoma database. However, it should be noted that Somerset's NDA 19,334 for Eldepryl Tablets was approved under orphan drug status and as such, the requested databases do not exist. In addition, Somerset's NDA 21,336 for Eldepryl Capsules was a reference application with bioequivalence data only. This application did not contain any controlled or long-term, open-label studies.

Somerset feels this information satisfies the Division's request. Please do not hesitate to contact me should any additional information be required.

Sincerely,

Melissa L. Goodhead, B.Sc., RAC
Director of Regulatory Affairs

:mlg

A Review of EMSAM Clinical Databases for Potential Association of EMSAM® Treatment with Malignant Melanoma

SUMMARY

Somerset Pharmaceuticals, Inc. has conducted a review of the selegiline transdermal safety databases specifically to detect any reported cases of melanoma. After an extensive search, as described below, no cases of malignant melanoma were reported.

1. OVERVIEW

For the purpose of this analysis, patient adverse event (AE) experiences following EMSAM® or placebo treatment were evaluated. This included patient data from controlled (double-blind) and uncontrolled (open-label) clinical studies in major depressive disorder, Alzheimer's disease, Parkinson's disease, [redacted], cocaine addiction, and HIV associated dementia databases. Adverse experiences were considered to have occurred either during EMSAM treatment or placebo treatment based on the onset date of the AE. Patient experience with placebo consists solely of data during double-blind study participation. A portion of these patients went on to receive EMSAM during open-label extension studies or, in the case of study S9303-P9806 (relapse prevention of depression), patients received EMSAM in the open-label period preceding the double-blind portion of the study. Therefore, patients reported in the EMSAM and placebo groups are not mutually exclusive. Since this analysis combines both long and short-term exposure data, and open-label and double-blind experience with EMSAM, a direct comparison to the short-term double-blind experience with placebo should not be inferred.

To determine a possible association of EMSAM therapy with malignant melanoma, patients were identified utilizing a set of specific AE search terms that was developed by the physician monitor whose task was to select and review all patient case report forms that warranted further evaluation. The physician monitor performed two levels of review for all patients in the aforementioned databases. The first level review (level-1 review) consisted of a computer-generated listing of patient data identified by AE search terms. No cases of malignant melanoma were generated by this level-1 review. Adverse events listings for three studies (S9303-E100-94B, S9303-E102-96B, and E110-97B) were reviewed in their entirety by the medical monitor due to the inability to access computerized databases. Based on a specific algorithm, patients were selected for comprehensive medical review (level-2 review) by the physician monitor. No cases of malignant melanoma were observed during this review.

2. METHODOLOGY

2.1 Level-1 Review

Somerset searched all safety databases for the possibility of an association with EMSAM treatment and malignant melanoma. The computer search of the databases included the following COSTART preferred terms:

- Carcinoma (body)
- Carcinoma skin
- Melanoma skin
- Neoplasm skin
- Granuloma skin

- Hypertrophy skin
- Skin disorder
- Skin discoloration

The listings generated by the search were initially reviewed by the physician monitor who was blind to treatment (level-1 review).

2.2 Level-2 Review

Adverse events were selected for comprehensive (level-2) medical review according to the following specific criteria generated by the medical monitor:

- All carcinoma (body) without a primary source
- All melanoma
- All skin carcinoma
- All moles
- Unexplained skin discoloration
- Undefined hyperkeratosis / Undefined skin lesions
- Any lesion of skin biopsied or removed with cryosurgery

Case report forms were reviewed by the medical monitor for all patients who reported an adverse event listed above.

3. RESULTS

3.1 Level-1 Results

There were 114 adverse events in the first level review. The search resulted in a listing that displayed the AE(s) of interest with dates and verbatim terms recorded during the study for each patient. After careful review of this AE listing by the physician monitor (level-1 review), 65 adverse events were determined not to meet criteria for further review. Using the algorithm described above, 50 adverse events were selected for comprehensive (level-2) review of case report forms. Thirty-eight adverse events were selected from a pool of 2467 EMSAM treated patients, and 12 adverse events were selected from a pool of 1240 placebo treated patients (see Table 1).

Table 1. Exposure of EMSAM/Placebo Patients in Phase II and Phase III Studies.

Study Number	Indication	N (STS/placebo)	Level-1 AEs (STS/placebo)	Level-2 AEs (STS/placebo)	Melanoma
Phase II studies					
S9303-E100-94B	Alzheimer's disease	70 (50/20)	1 (0/1)	1 (0/1)	0
S9303-E102-96B[2]	Parkinson's disease	25 (25/0)	0	0	0
S9303-E110-97B	HIV associated dementia	14 (9/5)	0	0	0
S9303-P9935[2]		20 (20/0)	0	0	0
S9303-E112-97B[2], S9303-P9937[1,2]		18 (18/0) 49 (49/0)	2 (2/0)	2 (2/0)	0
NIDA-1019	Cocaine addiction	300 (150/150)	10 (5/5)	1 (0/1)	0
Phase III studies					
S9303-E106-96B[1], S9303-E113-98B[1], S9303-E114-98B[1], S9303-P9804[1], S9303-P0052[1], S9303-P9806[1,5], S9303-P0204[2], S9303-P0043[2]	Depression	177 (89/88) 297 (147/150) 446 (300/146) 310 (153/157) 265 (132/133) 322 (159/163) 773 (773/0) 24 (24/0)	49 (47/2)	13 (12/1)	0[6]
S9303-E109-97B[1]	Parkinson's disease	191 (96/95)	5 (2/3)	5 (2/3)	0[6]
S9303-E101-96B[1]	Alzheimer's disease	406 (273/133)[3]	47 (31/15/1)[4]	28 (22/6)	0[6]
Total		3700 (2467/1240)	114 (87/26/1)	50 (38/12)	0

[1] Data from patients continuing in open-label follow-up studies are included.
[2] Open-label study
[3] 465 patients were enrolled, 273 were randomized to STS and 133 to placebo. 59 participated in a run-in placebo phase and were not randomized but were included in the search of the database.
[4] 31 patients were randomized to STS, 15 to placebo and 1 received no treatment.
[5] 675 patients began this study with a 10 week open label run in period. 322 were then randomized. All 675 patients were included in the database search.
[6] Results of AE's (four total) still under investigation.

3.2 Level-2 Results

Individual patients may have had more than one AE within the search strategy. The 46 patients selected by the algorithm had 50 adverse events of clinical interest. Table 2 summarizes the active and placebo level-2 results as a percentage of patients who reported one of the following adverse events; non-melanoma skin cancer, mole, hyperkeratosis/undefined skin lesion, or unexplained skin discoloration. In addition, the incidence rate of these adverse events is described as the number of events reported per 1,000 patient exposure days. No apparent difference was obtained between active and placebo treatment with the exception of "unexplained skin discoloration". The category "unexplained skin discoloration" is composed predominantly of miscoded COSTART terms and therefore, has little relevance in this analysis.

The 46 patients in the second level review had the following events:

- **19 non-melanoma skin cancers**
  Ten EMSAM-treated patients accounted for 13 adverse events consisting of 11 basal cell carcinomas and 2 squamous cell carcinomas. Of these 10 subjects, 4 had a prior history of skin cancer and a fifth subject (squamous cell carcinoma) had the lesion present at screening. Five placebo-treated subjects accounted for 6 adverse events consisting of 5 basal cell carcinomas and 1 squamous cell carcinoma. None of these patients had a prior history of skin cancer or positive physical findings at screening.

- **6 moles**
  Five EMSAM-treated patients had 5 adverse events reports of "mole". One case was not biopsied, but was considered benign by the investigator. Two moles were biopsied and determined to be benign, and results are currently unknown for the final two moles (see below). One placebo-treated patient reported an adverse event of "mole". This mole was removed by scraping and treated locally with hydrogen peroxide and bacitracin.

- **19 undefined hyperkeratosis/undefined skin lesions**
  Thirteen EMSAM-treated patients accounted for 14 adverse events, and 5 placebo-treated patients accounted for 5 adverse events consisting of various skin lesions, such as senile keratoses, fibrokeratoses, skin tags, sebaceous cysts and macular lesions treated with hydrocortisone. In the opinion of the physician monitor, none of these cases, in either the active or placebo groups, were related to melanoma.

- **6 unexplained skin discolorations**
  Four adverse events reported as skin discoloration were actually application site reactions that were miscoded. One adverse event was originally reported as a "sun spot" and coded to skin discoloration, but was later reported as a basal cell carcinoma and has been captured in the non-melanoma skin cancer portion of this discussion. The sixth patient had a verbatim term adverse event of "erythema" that for unexplained reasons was coded to skin discoloration.

Table 2. Level-2 Review of Adverse Events/Incidence Rates [Incidence/1000 patient days]

	STS (n=2467) [409,920 patient exposure/days]	Placebo (n=1240) [106,663 patient exposure/days]
Non-melanoma skin cancer	10(0.4%) [2.44]	5(0.4%) [4.69]
Mole	5(0.2%) [1.22]	1(0.08%) [.94]
Unidentified hyperkeratosis/ skin lesions	13(0.5%) [3.42]	5(0.4%) [4.69]
Unexplained Skin Discoloration	6(0.2%) [1.46]	0(0%) [0]

Particular attention was given to the 28 skin lesions that were biopsied or treated with cryosurgery. Results from the biopsies of 25 of these lesions are known and reveal no evidence of melanoma. The results for the following three cases are currently not known:

- Patient 15047 (Study S9303-P0204) – Actively treated with EMSAM. Mole biopsied on —. The Principal Investigator reported the following, "Patient had a long-standing mole on her arm that her PCP thought looked a little irregular, so it was removed. Patient never heard anything back from — about the biopsy report, so she assumed it was normal".

- Patient 0316 (Study S9303-E101-96B) – Actively treated with EMSAM. Skin lesions removed from face and hip.

- Patient 02008 (Study S9303-E109-97B) – Placebo treatment. Skin lesion.

Somerset is continuing to pursue information concerning these three cases. This information will be provided to the Agency when it becomes available.

4. CONCLUSION

A review of Somerset's entire Phase II and III safety databases was conducted to identify any reports of malignant melanoma. After a two-tiered evaluation, this review failed to reveal any cases of malignant melanoma.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 091
Expiration Date: February 29, 2

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee r can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

Somerset Pharmaceuticals, Inc.
2202 North West Shore Boulevard
Suite 450
Tampa, Florida 33607

2. TELEPHONE NUMBER *(Include Area Code)*

(813) 288-0040

3. PRODUCT NAME

EMSAM (Selegiline Transdermal System)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NO21708

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☑ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HI AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATI

☑ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

NO21336

(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4626

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☑ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for revie instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of informa Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Group Director, regulatory Affairs/QA	10/08/2003

FORM FDA 3397 (4/02)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Somerset Pharmaceuticals, Inc.	September 26, 2003
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(813) 288-0040	(813) 282-3804
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 2202 North West Shore Boulevard, Suite 450, Tampa, Florida 33607	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21,336

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Selegiline Transdermal System	EMSAM

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* | CODE NAME *(If any)*

DOSAGE FORM: Transdermal | STRENGTHS: 20mg/30mg/40mg | ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Major Depression

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Requested CMC Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 | THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*

- ☐ 1. Index
- ☐ 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☒ 4. Chemistry section
- ☒ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
- ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
- ☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- ☐ 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- ☐ 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- ☐ 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- ☐ 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- ☐ 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- ☐ 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- ☐ 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- ☐ 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- ☐ 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- ☐ 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)
- ☐ 15. Establishment description (21 CFR Part 600, if applicable)
- ☐ 16. Debarment certification (FD&C Act 306(k)(1))
- ☐ 17. Field copy certification (21 CFR 314.50(k)(3))
- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☐ 20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Melissa L. Goodhead	Melissa L. Goodhead Group Director, Regulatory Affairs/QA	09/26/03

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
2202 North West Shore Boulevard #450 Tampa, Florida 33607	(813) 288-0040

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Somerset
PHARMACEUTICALS, INC.

2202 N. West Shore Blvd., Suite 450
Tampa, Florida 33607
(813) 288-0040

September 26, 2003

Russell Katz, M.D.
Director, Division of Neuropharmacological
Drug Products (HFD-120)
FOOD AND DRUG ADMINISTRATION
Woodmont II
1451 Rockville Pike
Rockville, MD 20852

RE: NDA No. 21,336
SELEGILINE TRANSDERMAL SYSTEM- MAJOR DEPRESSION
Requested CMC Information: Revised Environmental Assessment
N: 036

Dear Dr. Katz:

Reference is made to Dr. Donald Klein's correspondence, dated September 22, 2003, requestin confirmation of Environmental Assessment-Categorical Exclusion with the addition of the 30mg and 40m STS. A revised Claim for Categorical Exclusion has been calculated and is enclosed. A copy of thi submission has been provided to Dr. Klein as a desk copy.

Should you require any additional information, please contact me at (813) 288-0040, extension 276.

Sincerely,

Melissa L. Goodhead

Melissa L. Goodhead, B.Sc., RAC
Group Director of Regulatory Affairs/Quality Assurance

:mlg

cc: Desk Copies:
Dr. Donald Klein
Dr. Doris Bates

2 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS
Somerset Pharmaceuticals, Inc.
2202 North West Shore Boulevard #450
Tampa, Florida 33607

2. TELEPHONE NUMBER *(Include Area Code)*
(813) 288-0040

3. PRODUCT NAME
Selegiline Transdermal System (EMSAM)

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER
4146

6. LICENSE NUMBER / NDA NUMBER
N021336

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Melissa L. Goodhead Melissa L. Goodhead	Director of Regulatory Affairs	05/07/01

FORM FDA 3397 (5/98)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

REQUEST FOR METHODS VALIDATION MATERIALS

NDA 21-336 &
NDA 21-708

Ms. Melissa Goodhead
Somerset Pharmaceuticals, Inc.
2202 North West Shore Blvd
Suite 450
Tampa, FL 33607

Dear Ms. Goodhead:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMSAM (Selegiline) Transdermal System, 20mg/20cm^2, 30mg/30cm^2 and 40mg/40cm^2

We will be performing methods validation studies on EMSAM (Selegiline) Transdermal System, 20mg/20cm^2 and 40mg/40cm^{2}as described in NDA 21-336 and NDA 21-708.

In order to perform the necessary testing, we request the following sample materials:

- Reference Standards:

- Drug Products:

Selegiline Transdermal System (20mg/20cm^2)	30 patches
Selegiline Transdermal System (40mg/40cm^2)	30 patches

- A copy of the latest test method, only if the methods submitted with the application to the Center have changed.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Duckhee Toler
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3866), FAX (314-539-2113), or email (duckhee.toler@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Duckhee Toler
Chemist
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

Duckhee Toler
1/19/2006 09:29:04 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REQUEST

TO: **FDA**
Division of Pharmaceutical Analysis, HFD-920
Attn: Nick Westenberger
Room 1002
1114 Market Street
St. Louis, MO 63101

FROM: Donald Klein, Reviewing Chemist, HFD-130
E-mail Address: kleind@cder.fda.gov
Phone: (301)-796-1689
Fax.: (301)-796-9749

Through: Thomas Oliver, Chemistry Team Leader, HFD-130
Phone: (301)-796-1728
and
Michael Folkendt, ONDC Methods Validation Coordinator, HFD-800
Phone: 301-827-5173

SUBJECT: Methods Validation Request

Application Number: NDA 21-336 and 21-708

Name of Product: EMSAM (selegiline) Transdermal System, 20 mg/20 cm2, 30 mg/30 cm2, and 40 mg/40 cm2

Applicant: Somerset Pharmaceuticals, Inc.

Applicant's Contact Person: Melissa Goodhead

Address: 2202 North West Shore Boulevard # 450, Tampa, Florida 33607

Telephone: 813-288-0040 Fax: 813-282-3804

Date NDA Received by CDER: **5/24/2001**
Date of Amendment(s) containing the MVP: **December 1, 2005**
DATE of Request: **December 15, 2005**
Requested Completion Date: **10/1/2006**
PDUFA User Fee Goal Date: **2/25/2006**

Chemical/Therapeutic Type: 3S
Special Handling Required: No
DEA Class: N/A

Format of Methods Validation Package
☒ Paper ☐ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request Form*. Upon receipt of the samples, perform the tests indicated in item 3 of the attached *Methods Validation Request Form* as described in the MV package. We request your report to be submitted in DFS promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the reviewing chemist of the date the validation process begins. If the requested completion date cannot be met, please promptly notify the reviewing chemist and the ONDC Methods Validation Coordinator.
Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying Methods Validation Report Summary). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DFS. Send the complete report, with the DFS signed *Methods Validation Report Summary*, by overnight courier to the above reviewing chemist. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

ATTACHMENT(S): *Methods Validation Request Form*, NDA Methods Validation Package (if not available in the EDR).

G

3 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Michael Folkendt
12/21/2005 03:39:41 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: JANUARY 18, 2002

To: **Russell Katz, M.D., Director**
Division of Neuropharmacological Drug Products (HFD-120)

Through: **Deborah B. Leiderman, M.D., Director**
Controlled Substance Staff (HFD-009)

From: **Katherine Bonson, Ph.D., Pharmacologist**
Controlled Substance Staff (HFD-009)

Subject: **Consultation on abuse potential of selegiline in transdermal delivery system, on proposed labelling and on potential for diversion of drug product to illicit laboratories**
NDA 21-336
EMSAM (selegiline transdermal system)
Treatment for depression
(Somerset Pharmaceuticals, Inc.)

Background:

Selegiline is an MAO inhibitor that preferentially inhibits the MAO-B form of the enzyme at therapeutically recommended doses. At higher doses, selegiline begins to inhibit both MAO-B as well as MAO-A. In the liver, selegiline is metabolized to a number of related compounds, including amphetamine and methamphetamine. It is this metabolic production of amphetamines that raises the possibility of abuse liability from selegiline use. However, the plasma levels of amphetamines resulting from oral administration of selegiline are not considered to be pharmacologically significant at therapeutic doses. Selegiline has never been controlled under the Controlled Substance Act.

Selegiline was approved for marketing by the FDA in 1989 under the trade name Eldepryl by Somerset Pharmaceuticals, Inc. under orphan drug status as an oral preparation for the treatment of Parkinson's disease. There are currently two generic preparations of selegiline in the US and 62 preparations marketed in foreign countries. The recommended daily dose of selegiline is 5 mg twice a day. The label for Eldepryl does not contain a drug abuse section, nor does it recommend against the administration of Eldepryl to individuals with drug abuse histories. The overdose section of the label

focuses on the risks of MAO-A inhibition and does not describe risks associated with the metabolic production of amphetamines from selegiline. Similarly, the adverse events section does not list central nervous system responses consistent with the effects of amphetamines.

Conclusion and Recommendations

* Transdermal administration of selegiline prevents the first pass effect, which exists with the oral formulation. This increases the plasma levels of selegiline and reduces the already small metabolic production of amphetamines.

* Transdermal administration of selegiline produces sustained plasma levels of selegiline over the 24 hour dosing period with minimal fluctuation. Abuse liability is more typically associated with the rapid onset of high plasma levels of a drug, followed by relatively rapid decreases. Thus, the slow onset and steady-state pharmacokinetics of transdermally administered selegiline would indicate a lower probability of drug abuse relative to oral selegiline.

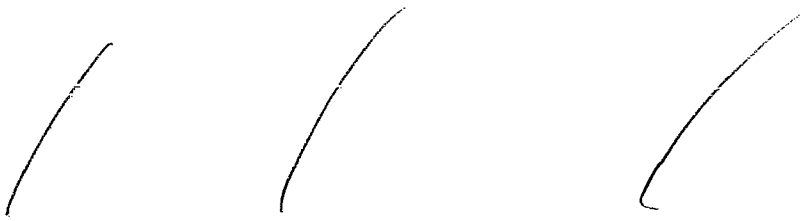
* There is no evidence of abuse problems with the oral preparations of selegiline. It is unlikely that the transdermal preparation has significant abuse liability.

* We are unaware of any reports that the oral preparation of selegiline is being used in street laboratories as a starting material for the synthesis of illicit amphetamines. Given that the synthetic process for conversion of selegiline to amphetamine is a difficult one, it is unlikely that the transdermal preparation of selegiline would be used for the illicit production of amphetamines.

Evaluation of Submitted Information and Epidemiology

The following was provided to CSS for evaluation: proposed labelling, and summaries of pharmacology, composition of drug product, pharmacokinetics/bioavailability, and drug abuse/overdose. In addition, the Integrated Summary of Safety and the Integrated Summary of Efficacy were submitted.

Proposed Label



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7 Page(s) Withheld

_____ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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

/s/

Katherine Bonson
1/18/02 03:08:53 PM
PHARMACOLOGIST

Deborah Leiderman
1/22/02 01:11:32 PM
MEDICAL OFFICER