

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-336/21-708

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-336
NDA 21-708

Melissa L. Goodhead, B.S., RAC
Group Director, Regulatory Affairs/Quality Assurance
Somerset Pharmaceuticals, Inc.
2202 N. West Shore Blvd., Suite 450
Tampa, FL 33607

Dear Ms. Goodhead:

Please refer to your new drug application (NDA) 21-336, dated May 24, 2001, received May 25, 2001, and to your New Drug Application (NDA) 21-708, dated October 15, 2003, received October 16, 2003, both submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for EMSAM (selegiline transdermal system) patches, 6mg/24 hours, 9mg/24 hours, and 12mg/24 hours.

We acknowledge receipt of your additional submissions dated December 21, 2004, January 20, 2005, May 26, 2005, June 9, 2005, June 17, 2005, June 21, 2005, July 18, 2005, July 21, 2005, August 2, 2005, August 16, 2005, August 31, 2005, October 4, 2005, October 10, 2005, November 3, 2005, November 15, 2005, November 16, 2005, January 9, 2006, February 6, 2006, and February 7, 2006.

Your May 26, 2005 submission, received May 27, 2005, constituted a complete, Class 2 response to our January 30, 2004 action letter for both referenced NDAs. Additionally, your November 16, 2005, submission constituted an extension on the regulatory due date.

These new drug applications provide for the use of EMSAM (selegiline transdermal system) patches, 6mg/24 hours, 9mg/24 hours, and 12mg/24 hours in the acute (21-336) and longer-term (21-708) treatment of major depressive disorder in adult patients.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling and Medication Guide. Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved NDAs 21-336 & NDA 21-708.**" Approval of these submissions by FDA is not required before the labeling is used.

All 15-day alert reports, periodic (including quarterly) adverse drug experience reports, field alerts, annual reports, supplements, and other submissions should be addressed to the original NDA, 21-336, for this drug product, not to NDA 21-708. In the future, do not make submissions to NDA 21-708 except for the final printed labeling requested above.

Pediatric Research Equity Act (PREA) Requirements-Studies Deferred

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving studies for ages 0 to 7 years (neonates and young children). We are deferring submission of your pediatric studies for ages 7 to 17 years (children and adolescents) until July 30, 2009.

Pediatric Exclusivity

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request" *in addition to* your plans for pediatric drug development described above. Please note that satisfaction of the requirements in Section 2 of PREA alone may not qualify you for pediatric exclusivity.

Dissolution Methods and Specifications

We note your agreement to accept the dissolution method and specifications requested for the dosage form. The agreed upon method and specification are presented here for reference:

Formulation(s)	6mg/24 hours (20 mg / 20 cm ²) (b) (4) and 2	12mg/24 hours (40 mg / 40 cm ²)
Media	----- ----- -----	----- ----- -----
Volume	-----	-----
Temp (°C)	-----	-----
Apparatus	----- -----	----- -----
RPM	-----	-----
Sampling Times And Specifications (% LC)	----- ----- ----- -----	----- ----- ----- -----
Acceptance Criteria	----- ----- -----	

Phase 4 Commitments

We remind you of your postmarketing commitments agreed upon in communications dated May 26, 2005 and January 18, 2006. These commitments are listed below.

1. Deferred pediatric studies under PREA

Your deferred pediatric study required under Section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of such postmarketing commitments shall be reported annually according to 21 CFR 314.81. The associated commitment is listed below.

You are required to assess the safety and effectiveness of EMSAM as a treatment for Major Depressive Disorder in pediatric patients ages 7 to 17 (children and adolescents). Both children (ages 7 to 11) and adolescents (ages 12 to 17) should be equally represented in the samples, and there should be a reasonable distribution of both sexes in these age strata.

Final Report Submission: July 30, 2009

Please submit final study reports to this NDA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment, whether submitted to the IND or the NDA, must be clearly designated "**Required Pediatric Study Commitments**".

2. Nonclinical Pharmacology and Toxicology: 2-year mouse carcinogenicity study (dermal route of application)

You are required to conduct a full 2-year carcinogenicity study of EMSAM in the mouse using the dermal route of application. Please refer to our action letter of January 30, 2004 for additional details regarding the need for this study. Please note that, as per the FDA Guidance "Special Protocol Assessment", the protocol for this study is eligible for special protocol review. Only one protocol at a time should be included in any submission for special protocol review, and each such protocol submitted should be submitted at least 90 days prior to the planned start of the study.

Final Report Submission: July 30, 2009.

3. Nonclinical Pharmacology and Toxicology: *in vivo* mouse micronucleus assay

You are required to conduct an *in vivo* mouse micronucleus assay either (a) via the oral route using a higher dose of selegiline in order to attain plasma exposures that cover the expected human plasma exposure or (b) via the dermal route. Please refer to our action letter of January 30, 2004 for additional details regarding the need for this study. Please note that, as per the FDA Guidance "Special Protocol Assessment", the protocol for this study is eligible for special protocol review. Only one protocol at a time should be included in any submission for special protocol review, each such protocol submitted should be submitted at least 90 days prior to the planned start of the study.

Final Report Submission: July 30, 2007.

4. Clinical Pharmacology and Biopharmaceutics: *Adhesion*

Please provide information regarding the adhesion properties of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm² to 40 cm²), over a 3 week period under conditions approximating actual use. The following factors are to be examined in this study:

- Subject age [i.e., young healthy adults, the elderly (65 – 84 years old), and the extreme elderly (> 85)].
- Application to the different labeled application sites including the upper torso and upper arm.
- For each study arm 100 completers are anticipated.
- The data generated should be examined by gender, race, physical activity, bathing and showering practices. Therefore variations in each of these secondary factors should be well represented in each study arm.

Within 3 months of approval Somerset will submit the protocols for these studies and will submit the final study reports within 9 months following the agreement on the protocols.

5. Clinical Pharmacology and Biopharmaceutics: *Dermal Tolerability*

Please provide information regarding the dermal tolerability of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm² to 40 cm²), over a 3 week period under conditions approximating actual use. The following factors are to be examined in this study:

- Subject age [i.e. young healthy adults, the elderly (65 – 84 years old), and the extreme elderly (> 85)].
- Application to the different labeled application sites including the upper torso and upper arm.
- For each study arm 100 completers are anticipated.
- The data generated should be examined by gender, race, physical activity, bathing and showering practices. Therefore variations in each of these secondary factors should be well represented in each study arm.

Within 3 months of approval Somerset will submit the protocols for these studies and will submit the final study reports within 9 months following the agreement on the protocols.

6. Clinical Pharmacology and Biopharmaceutics: *Performance of Selegiline Transdermal Systems in the Elderly*

Only 3 subjects studied were > 65 years of age. All three were women and the eldest was 70 years old. Consequently, please provide information regarding the pharmacokinetic, pharmacodynamic and biopharmaceutic properties of the selegiline transdermal system over the range of approved patch sizes, (i.e. 20 cm² to 40 cm²), in young healthy adults, the elderly (i.e. 65 – 84 years old), and the extreme elderly (i.e. > 85).

- The effects of gender and ethnicity/race should be examined for each age range.
- Information provided for each age group should include the following:
 - complete pharmacokinetic profiles of selegiline and the 3 metabolites previously examined
 - the tyramine response
 - MAO selectivity
 - drug delivery
 - safety information by age
- With regard to safety we are specifically interested in CNS effects, as well as differences in blood pressure changes, especially as the elderly typically have higher baseline systolic blood pressure and are at risk for orthostatic hypotension.

Within 3 months of approval Somerset will submit the protocols for these studies and will submit the final study reports within 9 months following the agreement on the protocols.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled

Comments and Recommendations on Risk Management Plan for EMSAM

Patient Education/Communication Tools (including the patient directed information to be placed on the unit-of-use packaging)

- The Medication Guide will be the main risk communication material for patients. All supplemental patient education pieces should reference the Medication Guide and/or contain identical language.
- A Wallet Card could be a useful tool; however, it may not be useful in its current form. There is a lot of information and the font size is quite small, and may not be readable for many patients. The font size of patient materials should be at least 10-point. The content should be limited to the concise key messages it is intended to convey, preferably in bulleted format.
- Since the prescriber will be responsible for the majority of the patient education, please ensure that prescribers are supplied with adequate teaching materials for their offices, including at minimum, the Wallet Card (with revisions as suggested above) and the Medication Guide.

Enhanced Pharmacovigilance Activities

- Section 3.2.1 'Spontaneous / Literature / Serious Clinical Trial Cases' (page # 12), mentions "creation of an algorithm to identify AEs of special interest related to hypertensive crisis and its complications". The algorithm was not included with this submission. Please submit the algorithm to the agency for possible comments.
- Section 3.2.2 'Targeted Adverse Event Follow-up' the RMP mentions that 'structured questionnaires will be designed to systematically collect targeted clinical and dietary intake information from spontaneous reports' of AEs of interest. Please submit to FDA the structured questionnaire that you plan to use for possible comments.
- Section 3.2.3

(b) (4)	(b) (4)
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- Reporting of Postmarketing Adverse Events

- We ask that you submit hypertensive crisis reports of any dosage strength as expedited reports pending further evaluation.
- The RMP mentions that routine signal detection activities will occur on a monthly basis (as detailed in the November 21, 2005 submission). Please include a summary of this information as a section in the quarterly report.
- Please send a desk copy of the quarterly report, via the usual method of sending desk copies, marked for "ODS".

Specialized Unit-of-Use Packaging

- We agree that specialized unit-of-use packaging would be useful in helping to deliver the dietary modification message and is also the best way to ensure that the patient receives the MG.
- The "**Dietary Modifications Required**" term, which appears in red lettering in a red box on the packaging, may not be understandable for some patients. We suggest revising this language to make it clearer, e.g., "**Important: Do not eat certain foods while using Emsam (see enclosed Medication Guide).**"

Education and Outreach Monitoring

You plan to conduct both physician and patient tracking surveys to assess the education and outreach efforts and indicate the results of such tracking will be reported to ODS at 9 and 15 month intervals following marketing. If physician and patient awareness of the primary risk communication message are below the pre-established goals for education and outreach, you indicate that you plan to create and implement a remediation plan to address deficiencies.

One of the patient tracking studies is described as a 2-wave quantitative survey among approximately 30 patients who received a prescription for Emsam, conducted at 6 and 12 months into the multi-layered education and outreach effort. The objective of the study will be to measure the percentage of patients receiving written information about Emsam risk management, the usefulness of patient materials received and the awareness of the key risk management messages. Please submit your complete protocol, when available, for further review and comment.

Comments and Recommendations on Container, Carton, and Patch Labeling

GENERAL COMMENTS

- The total drug amount per patch size (XX mg/XX cm²) may immediately follow the expression of strength per 24 hours or be located on the side panel for further clarification. If the total drug content per patch size will immediately follow the expression of strength per 24 hours, the total drug content per patch size should be given less prominence in order to avoid confusion.
- You have placed the statement "Dietary Modification Required" on the 9 mg/24 hours and 12 mg/24 hours container labels and carton labeling.
 - This statement should refer to the MedGuide where it is further defined.

- We are concerned that patients may double up with the 6 mg/24 hours patch for a 12 mg/24 hours dose yet not follow or be aware of the dietary restrictions since this strength is not labeled as such. To remedy this situation, we suggest that all packaging materials for the 6 mg/24 hours patch remind patients not to wear more than 1 patch at a time.

CONTAINER LABEL (Pouch)

- See GENERAL COMMENTS above
- The established name is difficult to read due to elongated font style and inadequate spacing between the letters. Please revise to increase the readability of the established name.
- The unit designation (i.e. mg, cm², and h) immediately follows the numbers without a space. Insert a space between the number and unit designation to improve readability.
- Relocate the expression of strength to follow the established name where it appears on each principal display panel.
- The pictorials on the back of the container label show a man wearing multiple patches. While DMETS realizes the intent of this pictorial is to show different proper sites for patch adhesion, it could be misinterpreted as a direction to place multiple patches on. DMETS prefers that arrows be used and that a title accompany the pictorial.
- The white writing on grey background for the 12 mg/24 hours strength is difficult to read. Please increase the background contrast by darkening the grey background.
- Include lot number and expiration date on the pouch label.

PATCH LABEL

- We acknowledge comments that your patch will have a “clear backer”. Reports in the literature describe cases of multiple patches being applied to hospitalized patients because of overlooked clear or translucent patches¹. To prevent adhesion of multiple patches, DMETS encourages use of visual cues, i.e., name and strength, such that old patches can be easily found for removal and are not overlooked. Additionally, consideration should be given to revising the patch so it has color. We acknowledge your comments that the patch label will be printed with white ink on a clear backer and that the black background represented by draft labeling is for viewing purposed only. Please ensure that there is sufficient contrast to afford adequate readability for the actual product once placed on the patient’s body.

¹ Institute for Safe Medication Practices Press Release: ISMP calls for more action to safeguard pain patches. August 13, 2005.

- We encourage the use of colors, boxing or some other means to differentiate the different strengths of the patches.
- Allow the established name to follow the proprietary name on the patch. We refer you to 21 CFR 201.10(g)(1) for guidance.

CARTON LABELING

- See GENERAL COMMENTS

PACKAGE INSERT LABELING

- See GENERAL COMMENTS
- HOW SUPPLIED

Include the established name of the drug product in association with the proprietary name where it appears in this section.

In addition, submit three copies of the introductory promotional materials that you propose to use for this/these product(s). Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division/ the Division of Psychiatry Products and two copies of both the promotional materials and the package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Renmeet Gujral, Pharm.D., Regulatory Project Manager, 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

Enclosure: Labeling and Medguide

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/s/

Thomas Laughren
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