CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-336/21-708

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

NDA 21-336
NDA 21-708

EMSAM® (selegiline) Transdermal System

Somerset Pharmaceuticals, Inc.

Chemistry Review

Donald N. Klein, Ph.D.

HFD-130

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-336 EMSAM® (selegiline) Transdermal System**
   NDA 21-708 EMSAM® (selegiline) Transdermal System

2. **CHEM. REVIEW: # 3 for NDA 21-336**
   CHEM. REVIEW: # 2 for NDA 21-708

3. **REVIEW DATE:** November 8, 2005.

4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** N21-336 Reviews # 1 and # 2; N21-708 Review # 1.

6. **SUBMISSION BEING REVIEWED:**

Submissions Reviewed	Document Date
Original	5/24/01
Amendment (MR)	1/29/03
Amendment (BC)	3/13/03
Resubmission (AZ)	7/31/03
Amendment (BC)	8/12/03
Information Request	8/13/03
Desk Copy (Original)	8/14/03
Amendment (BC) (2x)	8/18/03
Amendment (BC)	8/20/03
Amendment (BC)	9/4/03
Amendment (BC)	9/25/03
Amendment (BC)	9/26/03
Information Request	10/1/03
Desk Copy	10/29/03
Amendment (BC)	10/29/03
Amendment (BC)	1/15/04
Amendment (BC)	1/20/04
AE Letter	1/29/04
Memo to File	8/9/04
Request for Guidance	5/19/05
Response to Guidance Request	5/19/05
Desk Copy (7/31/03 Resubmission)	5/26/05
Desk Copy (5/26/03 Resubmission)	5/26/05
Resubmission (AZ)	5/26/05

Submissions Reviewed	Document Date
Status of Method Validation (E-mail)	5/27/05
Information Request (E-mail)	5/31/05
Response (E-mail)	5/31/05
Information Request (E-mail)	6/2/05
Response (E-mail)	6/2/05
Information Request (E-mail)	6/9/05
Response (E-mail)	6/9/05
Desk Copy	6/9/05
Amendment (BC)	6/9/05
Samples	6/10/05
Information Request (2 E-mails)	6/14/05
Information Request (2 E-mails)	6/16/05
Response (2 E-mails)	6/16/05
Desk Copy	6/17/05
Information Request (E-mail)	6/17/05
Amendment (BC)	6/17/05
Desk Copy	6/18/05
Amendment (BC)	6/18/05
Desk Copy	6/21/05
Response (E-mail)	6/21/05
Information Request (E-mail)	6/23/05
Response (E-mail)	6/24/05
Information Request (E-mail)	6/30/05
Information Request (E-mail)	7/1/05
Response (E-mail)	7/1/05
Information Request (E-mail)	7/6/05
Response (E-mail)	7/6/05
Response (E-mail)	7/7/05
Information Request (E-mail)	7/11/05
Response (E-mail)	7/11/05
Information Request (Telecon)	7/18/05
Amendment (BC)	7/18/05
Desk Copy	7/18/05
Information Request (E-mail)	7/21/05
Information Request (E-mail)	7/22/05
Response (E-mail)	7/27/05
Information Request (E-mail)	7/29/05

Submissions Reviewed	Document Date
Desk Copy	8/2/05
Amendment (BC)	8/2/05
Response (E-mail)	8/4/05
Update on CMC-Pharm/Tox Issues (E-mail)	8/5/05
Information Request (E-mail)	8/23/05
Response (E-mail)	8/23/05
Telecon	9/13/05
Information Request	9/13/05
Telecon	9/14/05
Information Request (2 E-mails)	9/14/05
Telecon	9/20/05
Response (E-mail)	9/21/05
Responses (2 E-mails)	10/4/05
Amendment (BC)	10/4/05
Response (E-mail)	10/5/05
Telecon	10/6/05
Information Request	10/6/05
Response (E-mail)	10/10/05
Amendment (BC)	10/10/05
Information Request (2 E-mails)	10/24/05
Response	10/31/05
Response	11/1/05
Amendment (BL)	11/3/05

7. NAME AND ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME:

Proprietary:	EMSAM®
Nonproprietary/USAN (2004):	selegiline
Code Name/Number:	1-deprenyl
Chem. Type/Ther. Class:	3S

9. LEGAL BASIS FOR SUBMISSION: Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50.

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** Antidepressant

11. **DOSAGE FORM:** Transdermal System (24 hours)

12 **STRENGTHS:** 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2

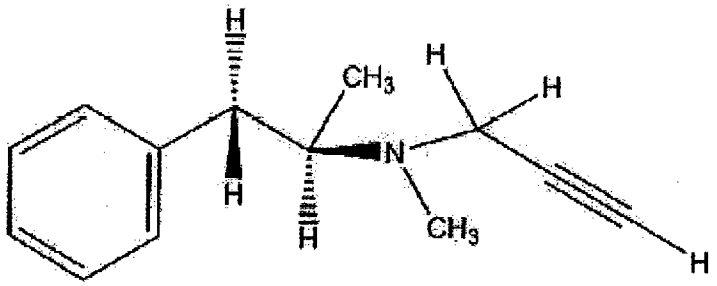
13. **ROUTE OF ADMINISTRATION:** Topical

14. **DISPENSED:** _x_ RX __OTC.

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): ___Yes _x_No.

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**
(-)-(*N*)-Methyl-*N*-[(1*R*)-1-methyl-2-phenylethyl]prop-2-yn-1-amine.

Molecular formula: $C_{13}H_{17}N$
Mol. Wt.: 187.30
CAS Registry: 14611-51-9



17. RELATED/ SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
[redacted]	II			3	Adequate	16-JAN-04	
[redacted]	II			3	Adequate	08-MAR-02	
[redacted]	IV			1	Adequate	07-NOV-05	
[redacted]	III			1	IR Letter Adequate	06-JUL-05 07-NOV-05	
[redacted]	III			1	Adequate	28-JUN-05	Secondary DMF in support of DMF
[redacted]	III			3	Adequate	25-SEP-01	Secondary DMF in support of DMF
[redacted]	III			1	Adequate	28-JUN-05	
[redacted]	III			3	Adequate	26-JAN-04	Secondary DMF in support of DMF
[redacted]	III			3	Adequate	16-JAN-04	
[redacted]	III			3	Adequate	14-JAN-04	
[redacted]	IV			1	Adequate	15-JUN-05	

[1]Action codes for DMF Table:

1--DMF Reviewed

Other codes indicate why the DMF was not reviewed, as follows:

2--Type 1 DMF
3--Reviewed previously and no revision since last review
4--Sufficient information in application
5--Authority to reference not granted
6--DMF not available
7—Other

[2]Adequate, Inadequate

B. Other Documents:

NDA or IND	Applicant or Sponsor	Drug Product and Indication	Date Approved or found Satisfactory
NDA 19-334	Somerset Pharmaceuticals	Eldepryl (selegiline HCl) Tablets, 5 mg; Parkinsons Disease	05-JUN-1989
NDA 20-647	Somerset Pharmaceuticals	Eldepryl (selegiline HCl) Capsules, 5 mg; Parkinsons Disease	15-MAY-1996
IND 46,944	Somerset Pharmaceuticals	Selegiline Transdermal System Depression	21-DEC-1994

18. STATUS:

Consults/ CMC Related Reviews	Recommendation	Date or Review #	Reviewer or Office
EES: N21-336 EES: N21-708	Acceptable Acceptable	17-JUN-2005 27-JUN-2005	Office of Compliance Office of Compliance
FDA Method Validation Report	Suitable for Control and Regulatory purposes	12-MAR-2004	St. Louis Laboratory
Memo to File	review status	09-AUG-2005	Donald Klein, Ph.D.
Methods Validation	Acceptable	08-NOV-2005	Division of Pharmaceutical Analysis, St. Louis, MO.
(Two new Methods)	To be sent to FDA Lab	*pending*	Division of Pharmaceutical Analysis, St. Louis, MO
Medical	Not Approvable Approval Approval Approvable *pending*	Review # 1 Review # 2 Memo to Review # 2 Review # 3 Review # 4	Gregory Dubitsky, M.D. Gregory Dubitsky, M.D. Thomas Laughren, M.D. Gregory Dubitsky, M.D. Gregory Dubitsky, M.D.
Microbiology	Acceptable	Review # 2	Stephen Langille, Ph.D.
OCPB	Acceptable *pending*	Review # 2 *pending*	Ronald Kavanagh, Ph.D. Ronald Kavanagh, Ph.D.
Environmental Assessment	Acceptable for 20 mg / 20 cm^2 Acceptable for 40 mg / 40 cm^2 Acceptable	Review # 1 Review # 2 08-NOV-2005	Richard Lostritto, Ph.D. Donald Klein, Ph.D. Donald Klein, Ph.D.
Pharm/Tox	Approvable Approvable *pending*	Review # 1 Review # 2 *pending*	Lois Freed, Ph.D. Paul Roney, Ph.D. Linda Fossom, Ph.D.
DMETS DDMAC	Acceptable	15-JUL-2005	DMETS DDMAC
CDER Transdermal Expert	specification should be at the lowest possible level or max.; composition in approved Transdermal Products (8 NDAs and 1 ANDA)	15-JUL-2005 04-OCT-2005	Amit Mitra, Ph.D.

The Chemistry Executive Summary

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-336 and NDA 21-708 for EMSAM® (selegiline) Transdermal System are recommended approval from the CMC standpoint.

B. Recommendations on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

The 1/29/04 AE Letter had the following two CMC deficiencies (underlined). After each deficiency is a summary of the response and a summary of issues addressed during this review cycle. It should be noted the applicant submitted 9 validation lots (3 of each dosage strength) with these Resubmissions. These validation lots were manufactured on commercial scale and had incorporated all the manufacturing changes discussed in Review # 2 (D.Klein, 1/29/04).

1. **1/29/04 AE Letter**: Include, as part of the drug product release specifications, a — for determining the — of selegiline. Please include a copy of the drug product — method and validation results in your complete response to this letter.

   Summary of Response and review cycle issues: The applicant revised the drug product specifications to include an — test —. The proposed new specification is NMT —% of — in the drug product. All of the 9 validation lots (3 of each dosage strength) met the NMT — specification. The — est method will be submitted for FDA laboratory validation

because the [redacted]

2. **1/29/04 AE Letter**: We note that your specified impurities [redacted] are suspected mutagens. Ideally, these impurities should not be present; however, if elimination is not possible, you need to reduce the amount of each impurity to a level not to exceed [redacted]. This limit was chosen, in part, based on the ICH Q3C guidance on residual solvents (Guidance for Industry, Q3C Impurities: Residual Solvents, December, 1997), which establishes a limit of 2 ppm for benzene, a known human carcinogen, and establishes limits of 4 to 8 ppm for several compounds labeled as possible or probable human carcinogens.

You must demonstrate that the amount of each of these potential mutagenic compounds does not exceed [redacted]. Lowering the level of each of these impurities to less than [redacted] would be preferable if the methodologies exist. Provide details of the method(s) [including limits of detection (LOD) and quantitation (LOQ)] used to evaluate the level of each impurity. Alternately, you could determine the genotoxic potential of [redacted] by directly testing these compounds in an *in vitro* gene mutation assay in bacteria (Ames test) and either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma tk assay (with colony sizing). These data would then be taken into consideration, in conjunction with other available data (e.g., published literature), in determining the need to lower the levels of these impurities.

Summary of Response and review cycle issues: In regards to the 4 [redacted] and the [redacted] impurity the applicant has tightened each of the 5 specifications to lowest possible level based on the 9 validation lots (3 of each dosage strength). As is outlined in this review, there has been much internal discussion (CDER Transdermal Expert and Pharm/Tox reviewer) along with negotiation with the applicant in order to reach acceptable specifications for these 5 compounds. The applicant's final specifications are as follows:

With these Resubmissions the applicant proposed a new analytical test method [redacted] for the quantification of the [redacted] and [redacted] in the drug product. This [redacted] method replaces the [redacted] method that had been found adequate (validated) by the FDA laboratory. The [redacted] test method will be validated by the FDA Lab because in comparison these methods [redacted] are significantly different with respect to the analytical equipment ([redacted] and [redacted] used.

Also, during this review cycle the description specification of the drug product was revised.

Eleven Drug Master Files were referenced in support of these NDAs and each has been found adequate.

All of the stability data (each dosage strength) met the revised Stability Specifications and based on the stability data a 24 month expiration date is granted.

The following drug product analytical test methods were found adequate by the FDA laboratory (12-MAR-2004): [redacted]

The drug product manufacturing site was found acceptable by Compliance.

Drug Substance

In the 1/29/04 AE Letter the only deficiency pertained to the acceptable level of the [redacted] impurity. The deficiency is presented in this Executive Summary's drug product section. As with the drug product, the applicant tightened the [redacted] impurity specification and for the drug substance the [redacted] Specification is NMT [redacted]. Based on the six drug substance lots evaluated in this review, this NMT [redacted] Specification cannot be lowered further based on current manufacturing.

During this review cycle the applicant provided the revised drug substance reference standard SOP. The applicant had committed to revise this SOP on 1/26/04.

The following drug substance analytical test methods were found adequate by the FDA laboratory (12-MAR-2004): [redacted]

The drug substance manufacturing site ([redacted]) was found acceptable by Compliance.

B. Description of How the Drug Product is Intended to be Used:

The packaging for the EMSAM® (selegiline) Transdermal System, 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2, is the [redacted] pouch material.

[redacted]). Each Transdermal system is packaged as a single unit in the [redacted] pouch. The transdermal system should be applied to dry skin on the upper torso, upper thigh, [redacted] once every 24 hours. The maximum daily dose is 40 mg.

In the **Storage and Disposal** section, the following statement is appropriate for the Transdermal dosage type: *Discard used EMSAM in household trash in a manner that prevents accidental application or ingestion by children, pets, or others.*

C. Basis for Approvable or Not-Approval Recommendation:

NDA 21-336 and NDA 21-708 (EMSAM® (selegiline) Transdermal System, Somerset Pharmaceuticals, Inc.) is recommended approval.

D. Administrative:

Reviewer, HFD-130: Donald N. Klein, Ph.D.
Team Leader, HFD-130: Thomas F. Oliver, Ph.D.
Project Manager, HFD-130: Doris Bates, Ph.D.

66 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/

Donald Klein
11/8/2005 08:46:47 AM
CHEMIST
Revised as discussed this morning.

Thomas Oliver
11/8/2005 08:55:45 AM
CHEMIST

NDA 21-708

EMSAM• •(selegiline) Transdermal System

Somerset Pharmaceuticals, Inc.

Chemistry Review

Donald N. Klein, Ph.D.
HFD-120

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CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-708 RESUBMISSION: EMSAM• •(selegiline) Transdermal System**
2. **CHEMISTRY REVIEW: # 1**
3. **REVIEW DATE:** January 29, 2004
4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** None

6. **SUBMISSION BEING REVIEWED:**

Submission Reviewed	Document Date
Original	15-OCT-03

7. **NAME AND ADDRESS OF APPLICANT:**

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

8. **DRUG PRODUCT NAME:**

Proprietary:	EMSAM• •
Nonproprietary/USAN [8/27/03]:	selegiline
Code Name/Number:	1-deprenyl
Chem. Type/Ther. Class:	3S

9. **LEGAL BASIS FOR SUBMISSION:** Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** Antidepressant (monoamine oxidase inhibitor (MAO))

11. **DOSAGE FORM:** Transdermal Patch (24 hours)

12 **STRENGTHS:** 20 mg/20 cm^2; 30 mg/30 cm^2; and 40 mg/40 cm^2

13. **ROUTE OF ADMINISTRATION:** Topical

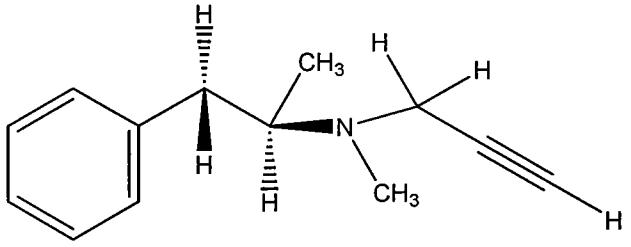
14. **DISPENSED:** x Rx __OTC

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): ___ Yes x NO

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**

Chemical Names: (R)-(-)-*N*-α-dimethyl-*N*-prop-2-ynylphenethylamine;
(R)-(-)-*N*-2-dimethyl-*N*-2-propynylphenethylamine

Molecular formula: $C_{13}H_{17}N$
Molecular Weight: 187.28
CAS Registry # : 14611-51-9



17. RELATED / SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
	II			Orig: 1 Resub: 7	Adequate N/A	08-MAR-02 N/A	Not revised since reviewed
	II			Orig: 1 Resub: 1	Adequate Adequate	08-MAR-02 16-Jan-04	**Resubmission:** Updated for the site change
	III			Orig: 1 Resub: 7	Adequate N/A	22-JAN-02 N/A	Not revised since reviewed; 7 replaces
	III			Orig: 1 Resub: 7	Adequate N/A	22-JAN-02 N/A	7 not in marketed product
	III			Orig: 7 Resub: 1,7[a]	Not present in DMF Adequate	N/A 16-JAN-04	7 Not present in DMF; 7[a] IR Letter dated 9/30/03; suitability data in resubmission; IR Letter dated 1/16/04
	III			Orig: 7 Resub: 7[a]	Adequate N/A	21-SEP-99 N/A	7 in marketed product; 7[a] not in marketed product
	IV			Orig: 1 Resub: 1, 7, 7[a]	Adequate Adequate	01-FEB-02 21-JAN-04	7 7, 7[a] Revised since reviewed; IR Letter dated 1/21/04
	III			Orig: N/A Resub: 1,7	N/A Inadequate Adequate	N/A 29-SEPT-03 14-JAN-04	Deficiency Letter dated 9/29/03; suitability data in resubmission
	III			Orig: 7 Resub: 1,7[a]	N/A Adequate	N/A 26-JAN-04	7 not submitted in original; 7[a] Replaces
	III			Orig: N/A Resub: 1,7	N/A Adequate	N/A 26-JAN-04	Secondary DMF in support of DMF
	IV			Orig: 3, 7 Resub: 7[a]	Adequate N/A	31-MAR-99 N/A	7 in marketed product; 7[a] not in marketed product
	IV			Orig: 3 Resub: 1	Adequate Adequate	05-JUL-99 29-SEPT-03	

[1]Action codes for DMF Table:

1--DMF Reviewed
Other codes indicate why the DMF was not reviewed, as follows:
2--Type 1 DMF
3--Reviewed previously and no revision since last review
4--Sufficient information in application
5--Authority to reference not granted
6--DMF not available
7--Other (explain under "Comments")

[2]Adequate, Inadequate

B. Other Documents:

NDA or IND	Applicant or Sponsor	Drug Product and Indication	Date Approved or found Satisfactory
NDA 19-334	Somerset Pharmaceuticals, Inc.	Eldepryl (selegiline HCl) Tablets, 5 mg; Parkinsons Disease	05-JUN-1989
NDA 20-647	Somerset Pharmaceuticals, Inc.	Eldepryl (selegiline HCl) Capsules, 5 mg; Parkinsons Disease	15-MAY-1996
IND 46,944	Somerset Pharmaceuticals, Inc.	Selegiline Transdermal System; Depression	21-DEC-1994

18. STATUS:

Consults / CMC Related Reviews	Recommendation	Date	Reviewer or Office
EES	Acceptable	10/30/03	Office of Compliance
Method Validation Package (N21-336 and N21-336 (RS))	Sent to FDA Lab on 9/12/03; FDA Lab contacted applicant on 12/17/03; Samples received on 12/30/03	*pending*	Division of Pharmaceutical Analysis, St. Louis, MO
Microbiology (N21-336 (RS))	Approval	11/12/03	Stephen Langille, Ph.D.
OCPB (N21-336 (RS))	Acceptable	1/14/04	Ronald Kavanagh, Ph.D.
Environmental Assessment (N21-336) (N21-336 (RS))	Acceptable for 20 mg/20 cm^2 Acceptable for 40 mg/40 cm^2	3/25/02 1/29/04	Richard Lostritto, Ph.D. Donald N. Klein, Ph.D.
Clinical (N21-336) (N21-336 (RS)) (N21-336 (RS))	Not Approvable Approval Approval	2/28/02 12/16/03 1/16/04	Gregory Dubitsky, M.D. Gregory Dubitsky, M.D. Thomas Laughren, M.D.
Pharm/Tox (N21-336) (N21-336 (RS))	Approvable *pending*	3/25/02 *pending*	Lois Freed, Ph.D. Paul Roney, Ph.D.

The Chemistry Review for NDA 21-708

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-708 for EMSAM• •(selegiline) Transdermal System is recommended approvable from the CMC standpoint. The approval for the CMC of this NDA is contingent on adequate responses to the CMC deficiencies related to the drug substance and drug product as outlined in the NDA 21-336 review # 2 dated January 29, 2004.

B. Recommendations on Phase 4(Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

The applicant references NDA 21-336 and NDA 21-336 Resubmission.

With the NDA 21-336 resubmission, the applicant added two new strengths, 30 mg/30 cm^2 and 40 mg/40 cm^2. Also, the applicant made the following CMC drug product changes:

1. (DMF) as the supplier of the
2. (DMF) as the
3. Discontinued the use of the (DMF

The composition of the EMSAM• •(selegiline) Transdermal system, 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2 is:

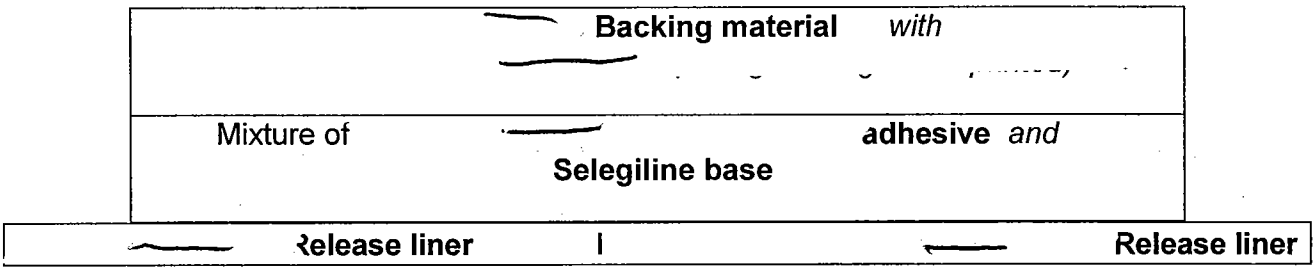
1. Drug substance ( ): Selegiline base
2. Adhesive
3. Release liner
4. Backing material
5.

The manufacturing process is identical for all three dosage strengths

The packaging for the EMSAM• •(selegiline) Transdermal system, 20 mg/20 cm^2, 30 mg/30 cm^2, and

40 mg/40 cm^2 is the [redacted] pouch material manufactured by the [redacted]

The diagram below is a cross-section of the Transdermal System.



With the NDA 21-336 Resubmission, the applicant had manufactured several drug product Lots in support of the following manufacturing changes or Specifications: (1) Addition of 2 new dosage strengths; (2) Use of the [redacted] release Liner; (3) Use of the [redacted] pouch manufactured by [redacted]; (4) Evaluation of the two impurities, [redacted] 5) Use of the [redacted] backing material; and, (6) Use of drug substance manufactured at the [redacted] site. Specifically:

1. Manufactured [redacted] different Lots of the 30 mg/30 cm^2 dosage strength and different Lots of the 40 mg/40 cm^2 dosage strength. Each of these [redacted] Lots are presently on stability testing.
2. One Lot of each dosage strength was manufactured with drug substance manufactured at the [redacted] site. Each of these 3 Lots are on stability testing.
3. Each of the dosage strengths have been manufactured with the [redacted] Backing:
   a. 20 mg/20 cm^2: [redacted] Lots (on stability).
   b. 30 mg/30 cm^2: [redacted] Lots (on stability).
   c. 40 mg/40 cm^2: [redacted] Lots (on stability).

4. Each of the dosage strengths have been manufactured with of the [redacted] release Liner:
   a. 20 mg/20 cm^2: [redacted] Lots (on stability).
   b. 30 mg/30 cm^2: [redacted] Lots (on stability).
   c. 40 mg/40 cm^2: [redacted] Lots (on stability).

5. The applicant conducted USP Testing along with stability testing (Suitability / Compatibility) to support the packaging change to the [redacted] Pouch manufactured by [redacted] Each of the dosage strengths have been packaged with the [redacted] Pouch:

a. 20 mg/20 cm^2: [redacted] Lots (on stability).
b. 30 mg/30 cm^2: [redacted] Lots (on stability).
c. 40 mg/40 cm^2: [redacted] Lots (on stability).

6. The applicant has manufactured several Clinical Lots:
   a. 20 mg/20 cm^2: [redacted] Lots (on stability).
   b. 30 mg/30 cm^2: [redacted] Lots (on stability).
   c. 40 mg/40 cm^2: [redacted] Lots (on stability).

The applicant had referenced 11 different Drug Master Files in support of this Resubmission, and each Drug Master File has been found adequate.

[redacted] impurities were first observed in the [redacted] experiment of the degradation study for the validation of [redacted], "Related Compounds for Selegiline Base", and [redacted] 'Related Compounds for Selegiline Transdermal Systems".

With the Resubmission the applicant proposed adequate specifications for the selegiline [redacted] impurities for the drug product. The applicant has shown that these impurities are not present in the drug substance upon release or on stability. In regards to the selegiline [redacted] the applicant provided adequate information: (1) Synthetic preparation; (2) Characterization data; (3) Analytical test method [redacted] was developed.

The Specifications (Regulatory and Stability) were tightened for the following Related Compounds: (1) [redacted] (2) [redacted] (3) [redacted] [redacted] (4) Total Impurities.

All of the stability data (3 ICH storage conditions) met the Stability Specifications as presented in the application, however, due to the nature of the drug substance and drug product deficiencies, the 24 month expiration date cannot be granted at this time.

The drug product manufacturing site was found acceptable by Compliance.

The applicant has adequately addressed the NDA 21-336 drug product CMC deficiencies presented in the March 25, 2002 NA Letter.

The NDA 21-336 and NDA 21-336 Resubmission Method Validation package was sent on 9/13/03 to the FDA Laboratory located in St. Louis, Missouri. After communication between the St. Louis lab personnel and Donald Klein, Ph.D. and Thomas Oliver, Ph.D., Somerset was contacted by the St. Louis lab analytical chemist on12/17/03. On 12/30/03 the St. Louis lab received the necessary method validation samples from the applicant. Because the manufacturing process is identical for all three dosage strengths [redacted], only the 20 mg/20 cm^2 dosage strength is undergoing the method validation, except for the Dissolution Test Method. Specifically, the Dissolution Test Method for the 40 mg/40 cm^2 is different than the Dissolution Test Method for the 20 mg/20 cm^2 and 30 mg/30 cm^2 transdermal system. Thus, both Dissolution Test Methods are being validated

by the St. Louis Lab.

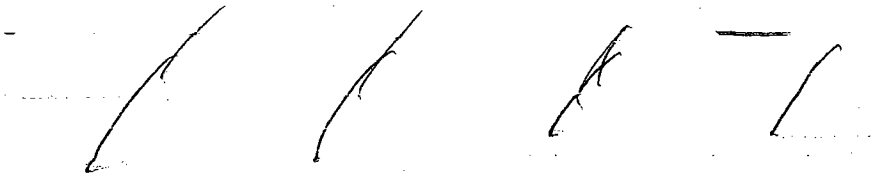
The two drug product issues that need to be addressed by the applicant are:

1. A — for determining the — of EMSAM• •(selegiline) is not present in the Drug Product Specifications.

2. Based on the Pharmtox opinion, the — impurity — — are specific mutagens. Ideally, these impurities should not be present; however, if elimination is not possible, either each impurity limit should be reduced to NMT — or the Total limit for these five impurities should be NMT —

Drug Substance

The applicant references NDA 21-336 and NDA 21-336 Resubmission.



With the NDA 21-336 resubmission the applicant had not yet applied to USAN in order to establish the drug substance "selegiline". A CMC Information Request Letter (August 13, 2003) asked the applicant to submit an USAN application. Subsequently, the applicant submitted an USAN application for "selegiline" on August 20, 2003. As a result, USAN registered "selegiline" on August 27, 2003.

In the original NDA 21-336 submission, — manufactured — was shipped to — At the — facility, — However, since the evaluation of the original NDA 21-336 submission, — As a consequence — site — carries out the complete drug substance manufacturing process. This manufacturing site change is presented in the NDA 21-336 Resubmission and the supportive DMF — has been (6/17/02) updated accordingly. DMF — was found Adequate on 1/16/04. As noted in Review # 1, DMF — was found adequate on March 8, 2002 for the manufacture of —

The applicant states the drug substance retest date is — . This was established in DMF —

The drug substance Reference Standard retest date is — . This was established via the applicant.

The drug substance manufacturing site [redacted] was found acceptable by Compliance.

The Clinical Pharmacology and Biopharmaceutics Review (Acceptable; R.Kavanagh, 1/14/04) states the change in the drug substance manufacturing site is acceptable to OCPB.

The applicant has adequately addressed the NDA 21-336 drug substance CMC deficiencies presented in the March 25, 2002 NA Letter.

On January 26, 2004, the applicant agreed to the following Commitment in regards to the SOP to manufacture the Drug Substance Reference Standard: *Revise the Drug Substance Reference Standard* [redacted] *procedure.*

The one drug substance issue that needs to be addressed by the applicant is:

1. Based on the Pharmtox opinion, the [redacted] impurity [redacted] is a mutagen.

B. Description of How the Drug Product is Intended to be Used

The packaging for the EMSAM•• (selegiline) Transdermal system, 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2 is the [redacted] pouch material. [redacted] Each Transdermal systems is packaged as a single unit in the [redacted] pouch. The transdermal system should be applied to dry skin on the upper torso, upper thigh, [redacted] once every 24 hours.

In the **STORAGE and DISPOSAL** section, the following statement is appropriate for the Transdermal dosage type: *Discard used EMSAM in household trash in a manner that prevents accidental application or ingestion by children, pets, or others.*

C. Basis for Approvable or Not-Approval Recommendation

NDA 21-708 (EMSAM•• Transdermal System, Somerset Pharmaceuticals, Inc.) is recommended approvable based on the CMC concerns relating to the drug substance and drug product. The deficiencies are detailed in the draft deficiency letter at the end of the NDA 21-336 Resubmission review # 2.

D. Administrative:
CMC Reviewer, Neuropharm Team 2: Donald N. Klein, Ph.D.
CMC Team Leader, Neuropharm Team 2: Thomas F. Oliver, Ph.D.
Project Manager: Doris Bates, Ph.D.

3 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/

Donald Klein
1/30/04 10:09:17 AM
CHEMIST

In pdf prior to DFS

Thomas Oliver
1/30/04 02:37:55 PM
CHEMIST

NDA 21-336 Resubmission

EMSAM® (selegiline) Transdermal System

Somerset Pharmaceuticals, Inc.

Chemistry Review

Donald N. Klein, Ph.D.
HFD-120

Table of Contents

CHEMISTRY NDA REVIEW DATA SHEET

1. **NDA 21-336 RESUBMISSION: EMSAM® (selegiline) Transdermal System**
2. **CHEMISTRY REVIEW: # 2**
3. **REVIEW DATE:** January 29, 2004
4. **REVIEWER:** Donald N. Klein, Ph.D.

5. **PREVIOUS DOCUMENTS:** None

6. **SUBMISSION BEING REVIEWED:**

Submission Reviewed	Document Date
Original	25-MAY-01
(MR) Amendment	29-JAN-03
(BC) Amendment	13-MAR-03
RESUBMISSION	31-JUL-03
(BC) Amendment	12-AUG-03
Information Request	13-AUG-03
Desk Copy (Original)	14-AUG-03
(BC) Amendment	18-AUG-03
(BC) Amendment	18-AUG-03
(BC) Amendment	20-AUG-03
(BC) Amendment	04-SEP-03
(BC) Amendment	09-SEP-03
(BC) Amendment	25-SEP-03
(BC) Amendment	26-SEP-03
Information Request	01-OCT-03
Desk Copy	29-OCT-03
(BC) Amendment	29-OCT-03
(BC) Amendment	15-JAN-04
(BC) Amendment	20-JAN-04

7. **NAME AND ADDRESS OF APPLICANT:**

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

8. **DRUG PRODUCT NAME:**

Proprietary:	EMSAM®
Nonproprietary/USAN [8/27/03]:	selegiline
Code Name/Number:	1-deprenyl
Chem. Type/Ther. Class:	3S

9. **LEGAL BASIS FOR SUBMISSION:** Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50

10. **PHARMACOLOGICAL CATEGORY/INDICATION:** Antidepressant (monoamine oxidase inhibitor (MAO))

11. **DOSAGE FORM:** Transdermal Patch (24 hours)

12. **STRENGTH:** 20 mg/20 cm², 30 mg/30 cm², and 40 mg/40 cm²

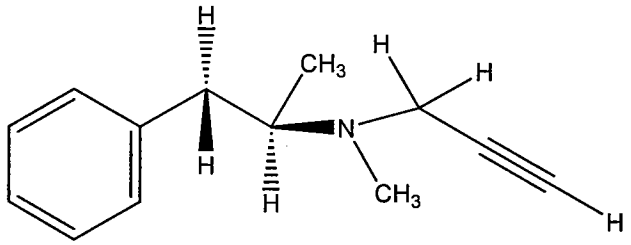
13. **ROUTE OF ADMINISTRATION:** Topical
3

14. **DISPENSED:** x Rx __OTC

15. **SPOTS** (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): ___ Yes x NO

16. **CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA:**
Chemical Names: (R)-(-)-*N*-α-dimethyl-*N*-prop-2-ynylphenethylamine;
(R)-(-)-*N*-2-dimethyl-*N*-2-propynylphenethylamine

Molecular formula: $C_{13}H_{17}N$
Molecular Weight: 187.28
CAS Registry # : 14611-51-9



17. RELATED / SUPPORTING DOCUMENTS:

A. DMF's:

DMF #	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
	II			Orig: 1 Resub: 7	Adequate N/A	08-MAR-02 N/A	Not revised since reviewed
	II			Orig: 1 Resub: 1	Adequate Adequate	08-MAR-02 16-Jan-04	**Resubmission:** Updated for the site change
	III			Orig: 1 Resub: 7	Adequate N/A	22-JAN-02 N/A	Not revised since reviewed; 7 replaces
	III			Orig: 1 Resub: 7	Adequate N/A	22-JAN-02 N/A	7 not in marketed product
	III			Orig: 7 Resub: 1,7[a]	Not present in DMF Adequate	N/A 16-JAN-04	7 Not present in DMF; 7[a] IR Letter dated 9/30/03; suitability data in resubmission; IR Letter dated 1/16/04
	III			Orig: 7 Resub: 7[a]	Adequate N/A	21-SEP-99 N/A	7 in marketed product; 7[a] not in marketed product
	IV			Orig: 1 Resub: 1, 7, 7[a]	Adequate Adequate	01-FEB-02 21-JAN-04	7 7, 7[a] Revised since reviewed; IR Letter dated 1/21/04
	III			Orig: N/A Resub: 1,7	N/A Inadequate Adequate	N/A 29-SEPT-03 14-JAN-04	Deficiency Letter dated 9/29/03; suitability data in resubmission
	III			Orig: 7 Resub: 1,7[a]	N/A Adequate	N/A 26-JAN-04	7 not submitted in original; 7[a] Replaces
	III			Orig: N/A Resub: 1,7	N/A Adequate	N/A 26-JAN-04	Secondary DMF in support of DMF
	IV			Orig: 3, 7 Resub: 7[a]	Adequate N/A	31-MAR-99 N/A	7 in marketed product; 7[a] not in marketed product
	IV			Orig: 3 Resub: 1	Adequate Adequate	05-JUL-99 29-SEPT-03	

[1]Action codes for DMF Table:

1--DMF Reviewed

Other codes indicate why the DMF was not reviewed, as follows:

2--Type 1 DMF

3--Reviewed previously and no revision since last review

4--Sufficient information in application

5--Authority to reference not granted

6--DMF not available

7--Other (explain under "Comments")

[2]Adequate, Inadequate

B. Other Documents:

NDA or IND	Applicant or Sponsor	Drug Product and Indication	Date Approved or found Satisfactory
NDA 19-334	Somerset Pharmaceuticals, Inc.	Eldepryl (selegiline HCl) Tablets, 5 mg; Parkinsons Disease	05-JUN-1989
NDA 20-647	Somerset Pharmaceuticals, Inc.	Eldepryl (selegiline HCl) Capsules, 5 mg; Parkinsons Disease	15-MAY-1996
IND 46,944	Somerset Pharmaceuticals, Inc.	Selegiline Transdermal System; Depression	21-DEC-1994

18. STATUS:

Consults / CMC Related Reviews	Recommendation	Date	Reviewer or Office
EES	Acceptable	8/18/03	Office of Compliance
Method Validation Package (N21-336 and N21-336 (RS))	Sent to FDA Lab on 9/12/03; FDA Lab contacted applicant on 12/17/03; Samples received on 12/30/03	*pending*	Division of Pharmaceutical Analysis, St. Louis, MO
Microbiology	Approval	11/12/03	Stephen Langille, Ph.D.
OCPB	Acceptable	1/14/04	Ronald Kavanagh, Ph.D.
Environmental Assessment	Acceptable for 20 mg/20 cm^2 Acceptable for 40 mg/40 cm^2	3/25/02 1/29/04	Richard Lostritto, Ph.D. Donald N. Klein, Ph.D.
Clinical	Not Approvable Approval Approval	2/28/02 12/16/03 1/16/04	Gregory Dubitsky, M.D. Gregory Dubitsky, M.D. Thomas Laughren, M.D.
Pharm/Tox	Approvable *pending*	3/25/02 *pending*	Lois Freed, Ph.D. Paul Roney, Ph.D.

The Chemistry Review for NDA 21-336

I. Recommendations:

A. Recommendations and Conclusions on Approvability.

NDA 21-336 for EMSAM® (selegiline) Transdermal System is recommended approvable from the CMC standpoint. The approval for the CMC of this NDA is contingent on adequate responses to the CMC deficiencies related to the drug substance and drug product as outlined in this review.

B. Recommendations on Phase 4(Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments:

A. Description of Drug Product and Drug Substance

Drug Product

With this resubmission, the applicant added two new strengths, 30 mg/30 cm^2 and 40 mg/40 cm^2. Also, the applicant made the following CMC drug product changes:

1. [redacted] (DMF [redacted] as the supplier of the [redacted]
2. [redacted] (DMF [redacted] as the [redacted]
3. Discontinued the use of the [redacted] (DMF [redacted]

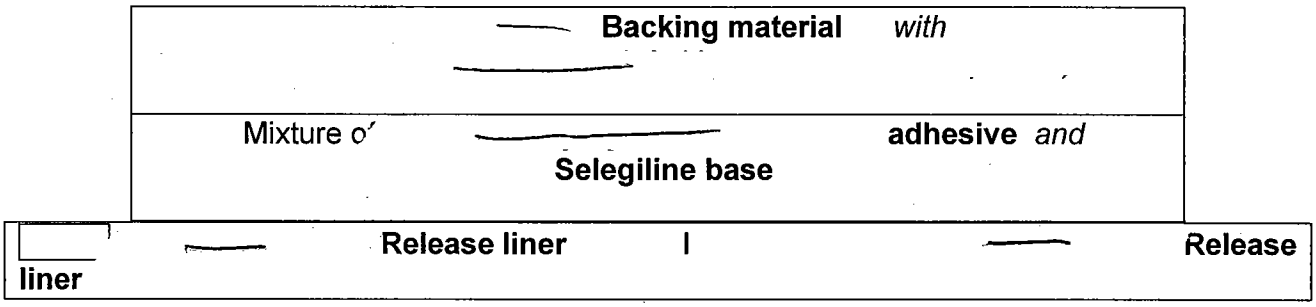
The composition of the EMSAM® (selegiline) Transdermal system, 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2 is:

1. Drug substance ([redacted]): Selegiline base [redacted]
2. Adhesive: [redacted]
3. Release liner [redacted]
4. Backing material [redacted]
5. [redacted]

The manufacturing process is identical for all three dosage strengths [redacted]

[redacted]. The packaging for the EMSAM® (selegiline) Transdermal system, 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2 is the [redacted] pouch material manufactured by the [redacted]

The diagram below is a cross-section of the Transdermal System.



With the Resubmission, the applicant had manufactured several drug product Lots in support of the following manufacturing changes or Specifications: (1) Addition of 2 new dosage strengths; (2) Use of the elease Liner; (3) Use of the pouch manufactured by (4) Evaluation of the two impurities, (5) Use of the backing material; and, (6) Use of drug substance manufactured at the site. Specifically:

1. Manufactured different Lots of the 30 mg/30 cm^2 dosage strength and different Lots of the 40 mg/40 cm^2 dosage strength. Each of these ots are presently on stability testing.
2. One Lot of each dosage strength was manufactured with drug substance manufactured at the Minden site. Each of these 3 Lots are on stability testing.
3. Each of the dosage strengths have been manufactured with the Backing:
    a. 20 mg/20 cm^2: Lots (on stability).
    b. 30 mg/30 cm^2: Lots (on stability).
    c. 40 mg/40 cm^2: Lots (on stability).

4. Each of the dosage strengths have been manufactured with of the Medirelease® 2249 release Liner:
    a. 20 mg/20 cm^2: Lots (on stability).
    b. 30 mg/30 cm^2: Lots (on stability).
    c. 40 mg/40 cm^2: Lots (on stability).

5. The applicant conducted USP Testing along with stability testing (Suitability / Compatibility) to support the packaging change to the Pouch manufactured by . Each of the dosage strengths have been packaged with the Pouch:
    a. 20 mg/20 cm^2: Lots (on stability).
    b. 30 mg/30 cm^2: Lots (on stability).

c. 40 mg/40 cm^2: 5 Lots (on stability).

6. The applicant has manufactured several Clinical Lots:
   a. 20 mg/20 cm^2: [redacted] Lots (on stability).
   b. 30 mg/30 cm^2: [redacted] Lots (on stability).
   c. 40 mg/40 cm^2: [redacted] Lots (on stability).

The applicant had referenced 11 different Drug Master Files in support of this Resubmission, and each Drug Master File has been found adequate.

[redacted] impurities were first observed in the [redacted] experiment of the degradation study for the validation of [redacted] "Related Compounds for Selegiline Base", and [redacted] 'Related Compounds for Selegiline Transdermal Systems".

With the Resubmission the applicant proposed adequate specifications for the selegiline [redacted] impurities for the drug product. The applicant has shown that these impurities are not present in the drug substance upon release or on stability. In regards to the selegiline [redacted] the applicant provided adequate information: (1) Synthetic preparation; (2) Characterization data; (3) Analytical test method [redacted] was developed.

The Specifications (Regulatory and Stability) were tightened for the following Related Compounds: (1) [redacted] (2) [redacted] (3) [redacted] (4) Total Impurities.

All of the stability data (3 ICH storage conditions) met the Stability Specifications as presented in the application, however, due to the nature of the drug substance and drug product deficiencies, the 24 month expiration date cannot be granted at this time.

The drug product manufacturing site was found acceptable by Compliance.

The applicant has adequately addressed the drug product CMC deficiencies presented in the March 25, 2002 NA Letter.

The Method Validation package was sent on 9/13/03 to the FDA Laboratory located in St. Louis, Missouri. After communication between the St. Louis lab personnel and Donald Klein, Ph.D. and Thomas Oliver, Ph.D., Somerset was contacted by the St. Louis lab analytical chemist on12/17/03. On 12/30/03 the St. Louis lab received the necessary method validation samples from the applicant. Because the manufacturing process is identical for all three dosage strengths [redacted], only the 20 mg/20 cm^2 dosage strength is undergoing the method validation, except for the Dissolution Test Method. Specifically, the Dissolution Test Method for the 40 mg/40 cm^2 is different than the Dissolution Test Method for the 20 mg/20 cm^2 and 30 mg/30 cm^2 transdermal system. Thus, both Dissolution Test Methods are being validated by the St. Louis Lab.

The two drug product issues that need to be addressed by the applicant are:

1. A [redacted] for determining the [redacted] of EMSAM® (selegiline) is not present in the Drug Product Specifications.

2. Based on the Pharmtox opinion, the [redacted] impurity [redacted] are specific mutagens. Ideally, these impurities should not be present; however, if elimination is not possible, either each impurity limit should be reduced to NMT [redacted] or the Total limit for these five impurities should be NMT [redacted]

Drug Substance

[redacted]

With this resubmission the applicant had not yet applied to USAN in order to establish the drug substance "selegiline". A CMC Information Request Letter (August 13, 2003) asked the applicant to submit an USAN application. Subsequently, the applicant submitted an USAN application for "selegiline" on August 20, 2003. As a result, USAN registered "selegiline" on August 27, 2003.

In the original submission, [redacted] manufactured [redacted] At the [redacted] facility [redacted]. However, since the evaluation of the original NDA submission, [redacted] As a consequence of [redacted] the site [redacted] carries out the complete drug substance manufacturing process. This manufacturing site change is presented in this Resubmission and the supportive DMF [redacted] has been (6/17/02) updated accordingly. DMF [redacted] was found Adequate on 1/16/04. As noted in Review # 1, DMF [redacted] was found adequate on March 8, 2002 for the manufacture of [redacted]

The applicant states the drug substance retest date is [redacted] This was established in DMF [redacted]

The drug substance Reference Standard retest date is [redacted] This was established via the applicant.

The drug substance manufacturing site [redacted] was found acceptable by Compliance.

The Clinical Pharmacology and Biopharmaceutics Review (Acceptable; R.Kavanagh, 1/14/04) states the change in the drug substance manufacturing site is acceptable to OCPB.

The applicant has adequately addressed the drug substance CMC deficiencies presented in the March 25, 2002 NA Letter.

On January 26, 2004, the applicant agreed to the following Commitment in regards to the SOP to manufacture the Drug Substance Reference Standard: *Revise the Drug Substance Reference Standard SOP with a*

The one drug substance issue that needs to be addressed by the applicant is:

1. Based on the Pharmtox opinion, the impurity is a mutagen.

B. Description of How the Drug Product is Intended to be Used

The packaging for the EMSAM® (selegiline) Transdermal system, 20 mg/20 cm^2, 30 mg/30 cm^2, and 40 mg/40 cm^2 is the pouch material. Each Transdermal systems is packaged as a single unit in the pouch. The transdermal system should be applied to dry skin on the upper torso, upper thigh, once every 24 hours.

In the **STORAGE and DISPOSAL** section, the following statement is appropriate for the Transdermal dosage type: *Discard used EMSAM in household trash in a manner that prevents accidental application or ingestion by children, pets, or others.*

C. Basis for Approvable or Not-Approval Recommendation

NDA 21-336 (EMSAM® Transdermal System, Somerset Pharmaceuticals, Inc.) is recommended approvable based on the CMC concerns relating to the drug substance and drug product. The deficiencies are detailed in the draft deficiency letter at the end of this review.

D. Administrative:
CMC Reviewer, Neuropharm Team 2: Donald N. Klein, Ph.D.
CMC Team Leader, Neuropharm Team 2: Thomas F. Oliver, Ph.D.
Project Manager: Doris Bates, Ph.D.

63 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

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/s/

Donald Klein
1/29/04 10:51:20 AM
CHEMIST

Thomas Oliver
1/29/04 01:19:50 PM
CHEMIST
Comment #3 should be deleted from the letter

NDA 21-336

EMSAM™ 20 mg/20 cm^2
Selegiline Transdermal System

Somerset Pharmaceuticals, Inc.

Richard T. Lostritto, Ph.D.
HFD-120 Division of Neuropharmacological Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-336

2. REVIEW #1:

3. REVIEW DATE: March 22,2002

4. REVIEWER: Richard T. Lostritto, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 46, 944	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA submission	March 25, 2001

7. NAME & ADDRESS OF APPLICANT:

Name:	Somerset Pharmaceuticals, Inc.
Address:	2202 North West Shore Boulevard Suite 450 Tampa, Florida 33607
Representative:	Melissa Goodhead
Telephone:	813-288-0040 extension 276

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: EMSAM
b) Non-Proprietary Name (USAN): selegiline
c) Code Name/# none used
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: fulfilled PDUFA filing requirements

10. PHARMACOL. CATEGORY: MAO Inhibitor

11. DOSAGE FORM: Transdermal Patch

12. STRENGTH/POTENCY: 20 mg/20 cm^2

13. ROUTE OF ADMINISTRATION: Topical

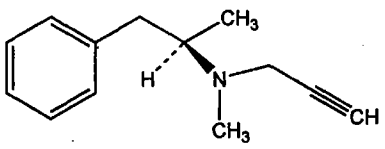
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Selegiline

Name	**Selegiline**
Chemical Name	(R)-(-)-N,-α-dimethyl-N-prop-2-ynylphenethylamine
CAS number	14611-51-9
Molecular Weight	187.28
Molecular Formula	$C_{13}H_{17}N$
Structural formula	Page 781 USAN 2001

17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COM-PLETED	COM-MENTS
	II			1	**Adequate**	01-MAR-02	None
	II			1	**Adequate**	01-MAR-02	None
	V			3	**Adequate** **Adequate**	31-MAR-99 05-JUL-96	Review dates for [redacted] shown
	III			1	**Adequate**	22-JAN-02	None
	III			1	**Adequate**	01-FEB-02	None
	IV			3	**Adequate**	21-SEP-99	None
	III			1	**Adequate**	01-FEB-02	None

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: NONE

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Clinical (efficacy)	**NOT APPROVABLE**	28-FEB-02	Greg Dubitsky
EES	Acceptable	15-MAR-02	
Pharm/Tox	Pending	n.a.	Lois Freed
Biopharm	Acceptable	28-FEB-02	Iftekhar Mahmood
LNC	Acceptable	24-JAN-02	
Methods Validation	Pending		
OPDRA	Pending		
EA	Categorical Exclusion Acceptable	22-MAR-02	Richard Lostritto
Microbiology	n.a.		

The Chemistry Review for NDA 21-336

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is APPROVABLE. There are deficiencies related to drug substance, drug product, and labeling. However, it is known from the Medical Officer's efficacy review dated 2/28/02, that the action to be taken on this application will be NOT APPROVABLE due to lack of efficacy

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

None at this time. The action on this application will be NOT APPROVABLE based on lack of efficacy (2/28/02)

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Selegiline is a well known and well characterized drug substance which was first reported in Chem Abstracts in 1965 and patented in 1966 (Netherlands).

Selegiline is: (R)-(-)-N,-α-dimethyl-N-prop-2-ynylphenethylamine with CAS registry number 14611-51-9 is a [redacted] Selegiline is the R enantiomer only.

The EMSAM selegiline transdermal system (20 mg/20cm^2) is a rectangular patch with rounded corners. It consists of a uniform, drug loaded contact adhesive coated on one side of a translucent backing. The adhesive-drug matrix is protected by a release liner which is removed at the time of application to the skin. The other side of the translucent backing has a [redacted] A schematic representation of the structure of the EMSAM drug product is depicted below.

Translucent backing layer	← Outer surface
Adhesive + selegiline base matrix	← Skin contact surface
Release liner	← Removed at time of application

Each patch is contained in a square, flat pouch which is notched with white paper on both sides. The pouch is imprinted with the lot number and manufacture date.

During manufacture, [redacted]

During later development, the applicant changed the color of the backing laminate (the part visible when applied) ***from*** [redacted] ***to the to-be-marketed clear backing*** [redacted] since the adhesive/drug matrix is clear, the entire to-be-marketed patch should be essentially transparent to translucent The only difference between these two backings is the color of the outermost layer. As described in the stability assessment section of this review, this minor change does not affect the applicant's shelf-life proposal of 24 months.

B. Description of How the Drug Product is Intended to be Used

The patient is to apply a single patch every 24 hours at about the same time each day, to the upper torso. ***At the time of removal, there will be approximately 15 mg of selegiline in the patch*** which is available if the patch or its contents were ingested by a human or animal.

C. Basis for Approvability Recommendation

There are deficiencies in the drug substance and drug substance reference standard related to specifications. There are deficiencies in the various [redacted] related to acceptance criteria. There are deficiencies in the drug product related to specifications and labeling.

Based on these deficiencies, this application is approvable from a CMC perspective

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Richard T. Lostritto, Ph.D. 21-MAR-02
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

27 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

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/s/

Richard Lostritto
3/25/02 11:06:11 AM
CHEMIST

Hasmukh Patel
3/25/02 11:38:44 AM
CHEMIST