CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20647/S001/S002/S003

Trade Name: ELDEPRYL 5 MG

Generic Name: SELEGILINE

Sponsor: SOMERSET PHARMACEUTICALS, INC

Approval Date: 08/06/97

Indication(s): ADJUNCT TREATMENT OF PARKINSONIAN PATIENTS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20647/S001/S002/S003

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20647/S001/S002/S003

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-647/S-001, S-002, S-003
NDA 19-334/S-010, S-013, S-014, S-015, S-016, S-017

Somerset Pharmaceuticals, Inc.
Attention: Cheryl Blume, Ph.D.
5415 West Laurel Street
Tampa, FL 33607

AUG 6 1997

Dear Dr. Blume:

Please refer to your May 5, 1992 (NDA 19-334/S-010), June 29, 1994 (NDA 19-334/S-013), November 30, 1995 (NDA 19-334/S-014), October 10, 1996 (NDA 20-647/S-001 and NDA 19-334/S-015), and December 23, 1996 (NDA 20-647/S-002 and NDA 19-334/S-016) supplemental new drug applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Eldepryl (selegiline) 5 mg tablets and capsules.

The supplemental applications provide for product labeling changes.

We note that your additional supplemental applications submitted on May 6, 1997 supersede these applications. Therefore, we will not review these supplement applications but they will be retained in our files.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling submitted on May 6, 1997. Accordingly, these supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact Ms. Teresa Wheelous, Regulatory Management Officer, at (301) 594-2777

Sincerely yours,

/S/ 8/4/97

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

cc:

APPEARS THIS WAY
ON ORIGINAL

Original NDAs 20-647, 19-334
HFD-120/Div. Files
HF-2/Medwatch (with labeling)
HFD-101/Office Director (with labeling)
HFD-120/RKatz /S/ 7/31/97
HFD-120/JSherry /S/ 8/01/97
HFD-120/CSO/T.Wheelous /S/ 8/4/97
HFD-40/DDMAC (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFD-560/OTC (with labeling - for OTC Drug Products Only

APPEARS THIS WAY
ON ORIGINAL

Drafted by: tw/July 16, 1997/c:\wheelous\nda\eldepryl-cp\slr003.ltr
Initialed by:
final:

ACKNOWLEDGE AND RETAIN (AR)/APPROVAL(AP)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20647/S001/S002/S003

MEDICAL REVIEW(S)

JUN 9 1997

FDA

Review and Evaluation of Clinical Data

NDA	**20-647**
Sponsor:	**Somerset Pharmaceuticals, Inc.**
Drug:	**Eldepryl ® (Selegiline hydrochloride) Capsules, 5 mg.**
Proposed Indication:	**Parkinson's Disease**
Material Submitted:	**Labeling Changes**
Serial No.:	**SLR-003**
Correspondence Date:	**May 6, 1997**
Date Received / Agency:	**May 16, 1997**
Date Received / Reviewer:	**May 27, 1997**
Date Review Completed	**May 30, 1997**

Introduction

The agency had previously requested (letter dated May 15, 1996; teleconference of October 3, 1996; letter dated February 7, 1997) that the sponsor revise the current labeling to include reports of hypertensive reactions associated with selegiline. One case involved a hypertensive reaction when selegiline was administered in conjunction with a sympathomimetic, ephedrine. Two other cases involved hypertensive reactions ("cheese reactions") associated with ingestion of tyramine containing foods while taking selegiline at a dose of 5 mg po BID. In the correspondence (Labeling Changes and Doctor Notification) of January 2, 1997 the sponsor made the requested changes to the Warnings, Information for Patients, and Precautions sections, however, through a miscommunication between the agency and the sponsor, the changes to the Clinical Pharmacology section were not completed. In the letter of February 7, 1997, the agency indicated that the sponsor should amended the clinical pharmacology section and that the labeling changes should be reflected in the labeling for both Eldepryl ® capsules and tablets.

Labeling Changes Requested

1 Page(s) Redacted

DRAFT LABELING

Recommendations:

1. **The labeling changes have been made for Eldepryl ® capsules.**
2. **Information has been entered in to the reviewer's database.**
3. **No additional action is required.**

/S/

James H. Sherry, M.D., Ph.D.
Medical Reviewer

cc:
HFD-120
HFD-120/Leber/Katz/Sherry

JAN - 9 1997

FDA

Review and Evaluation
of Clinical Data

NDA	**20-647 / 19-334**
Sponsor:	**Somerset Pharmaceuticals, Inc.**
Drug:	**Eldepryl ® (Selegiline hydrochloride) Capsules, 5 mg. / Tablets, 5 mg.**
Proposed Indication:	**Parkinson's Disease**
Material Submitted:	**Labeling Changes and Doctor Notification Letter**
Serial No.:	**NC / SLR-002 / SLR-016**
Correspondence Date:	**January 2, 1997**
Date Received / Agency:	**January 3, 1997**
Date Received / Reviewer:	**January 4, 1997**
Date Review Completed	**January 9, 1997**

APPEARS THIS WAY
ON ORIGINAL

Introduction

The agency had previously requested that the sponsor revise the current labeling to include reports of hypertensive reactions associated with selegiline. One case involved a hypertensive reaction when selegiline was administered in conjunction with a sympathomimetic, ephedrine. Two other cases involved hypertensive reactions ("cheese reactions") associated with ingestion of tyramine containing foods while taking selegiline at a dose of 5 mg po BID. In addition, due to the nature of these reactions, the sponsor was asked to prepare a physician notification letter.

APPEARS THIS WAY
ON ORIGINAL

Doctor Notification

Somerset Pharmaceuticals, Inc.("Somerset") manufactures and markets Eldepryl ® Capsules (Selegiline HCl) for use as adjunctive therapy in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy.

Somerset calls to your attention new safety information that has recently been included in the Clinical Pharmacology, Warnings, Information for Patients, and Precautions sections of the Eldepryl ® product labeling. The revised labeling notes hypertensive reactions have occurred in patients receiving Eldepryl ® at the recommended dose (5mg bid) associated with ingestion of tyramine containing foods. One case of a hypertensive crisis has been reported in a patient on the recommended dose of selegiline treated with a concomitant sympathomimetic medication. A more detailed description of this event can be found in Clinical Endocrinology, "Pseudo-phaeochromocytoma after multiple drug interactions involving the selective monoamine inhibitor selegiline", (1995) 42, 95-99. Although these reports are incomplete and do not constitute conclusive proof that the observed hypertension resulted from Eldepryl ®, it is prudent to include this information with our labeling.

APPEARS THIS WAY
ON ORIGINAL

While hypertensive events are rarely encountered when the labeled Eldepryl ® dose regimen is employed, these risks significantly increase when patients are exposed to higher doses. Accordingly, careful monitoring is required for patients who are prescribed Eldepryl ® in doses exceeding 10mg per day and for those patients who are transferred from one selegiline preparation to another.

Labeling Changes

Recommendations:

1. **The Doctor Notification Letter is satisfactory.**
2. **The changes to the Warnings, Information for Patients, and Precautions sections are satisfactory.**
3. **The clinical pharmacology section should be amended as written above.**
4. **These labeling changes should be reflected in the labeling for both Eldepryl® capsules and tablets.**

/S/

James H. Sherry, M.D., Ph.D.
Medical Reviewer

cc:
HFD-120
HFD-120/Leber/Katz/Sherry

/S/ 1/9/97

OCT 22 1996

FDA

Review and Evaluation of Clinical Data

NDA	**20-647**
Sponsor:	**Somerset Pharmaceuticals, Inc.**
Drug:	**Eldepryl ® (Selegiline hydrochloride) Capsules, 5 mg.**
Proposed Indication:	**Parkinson's Disease**
Material Submitted:	**Labeling Changes and Doctor Notification Letter**
Serial No.:	**SLR-001 / Supplement 03**
Correspondence Date:	**October 10, 1996**
Date Received / Agency:	**October 11, 1996**
Date Received / Reviewer:	**October 14, 1996**
Date Review Completed	**October 17, 1996**

Introduction

The agency had previously requested (letter dated May 15, 1996; teleconference of October 3, 1996) that the sponsor revise the current labeling to include reports of hypertensive reactions associated with selegiline. One case involved a hypertensive reaction when selegiline was administered in conjunction with a sympathomimetic, ephedrine. Two other cases involved hypertensive reactions ("cheese reactions") associated with ingestion of tyramine containing foods while taking selegiline at a dose of 5 mg po BID. In addition, due to the nature of these reactions, the sponsor was asked to prepare a physician notification letter.

Draft Labeling

1 Page(s) Redacted

DRAFT LABELING

Doctor Notification

Somerset Pharmaceuticals, Inc.("Somerset") manufactures and markets Eldepryl ® Capsules (Selegiline HCl) for use as adjunctive therapy in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy.

Somerset calls to your attention new safety information that has recently been included in the Clinical Pharmacology, Warnings, Information for Patients, and Precautions sections of the Eldepryl ® product labeling. The revised labeling notes hypertensive reactions have occurred in patients receiving Eldepryl ® at the recommended dose (5mg bid) associated with ingestion of tyramine containing foods. One case of a hypertensive crisis has been reported in a patient on the recommended dose of selegiline treated with a concomitant sympathomimetic medication. A more detailed description of this event can be found in Clinical Endocrinology, "Pseudo-phaeochromocytoma after multiple drug interactions involving the selective monoamine inhibitor selegiline", (1995) 42, 95-99. Although these reports are incomplete and do not constitute conclusive proof that the observed hypertension resulted from Eldepryl ®, it is prudent to include this information with our labeling.

While hypertensive events are rarely encountered when the labeled Eldepryl ® dose regimen is employed, these risks significantly increase when patients are exposed to higher doses. Accordingly, careful monitoring is required for patients who are prescribed Eldepryl ® in doses

exceeding 10mg per day and for those patients who are transferred from one selegiline preparation to another.

For your convenience, Somerset has enclosed the revised labeling for Eldepryl® Capsules.

/S/

James H. Sherry, M.D., Ph.D.
Medical Reviewer

cc:
HFD-120
HFD-120/Leber/Katz/Sherry

/S/ 10/22/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20647/S001/S002/S003

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

JUL 16 1997

Division of Neuropharmacological Drug Products, HFD-120

REGULATORY MANAGEMENT OFFICER REVIEW

Application Number: [redacted] and 19-334
Name of Drug: Eldepryl capsules 5mg and Eldepryl tablets 5 mg
Sponsor: Somerset Pharmaceuticals, Inc.

Material Reviewed

Submission Date(s): May 5,1992 (NDA 19-334/S-010), June 29,1994 (NDA 19-334/S-013), November 30,1995 (NDA 19-334/S-014), June 3, 1996 (NDA 20-647/S-000), October 10,1996 (NDA 20-647/S-001 and NDA 19-334/S-015), and December 23,1996 (NDA 20-647/S-002 and NDA 19-334/S-016) and May 6, 1997 (NDA 19-334/S-017 and NDA 20-647/S-003)

Background and Summary Description:
On May 15, 1996 an approval letter issued for Eldepryl capsules 5mg. On February 7, 1997 an Agency letter issued requesting the sponsor to make specific changes to labeling for both Eldepryl capsules and tablets. The May 6, 1997 supplement is the sponsor's response to the requested labeling changes.

Review:
I compared the May 15, 1996 Eldepryl capsules approval labeling (ELD:R9) to the May 6, 1997 labeling supplement (SLR-003) the differences from the original approval labeling are as follows:

1. CLINICAL PHARMACOLOGY SECTION 5th para, 2nd sentence.
   Addition: Although rare, a few reports of hypertensive reactions have occurred in patients receiving Eldepryl at recommended dose, with tyramine-containing foods. In addition
   Deletion: the word "However" in the 3rd sentence.

2. CLINICAL PHARMACOLOGY section 6th paragraph
   Addition: two words,"few" and "cases"
   Deletion: one word, "case"

3. WARNINGS section 2nd para. 2nd sentence.
   Addition: Rare cases of hypertensive reactions associated with ingestion of tyramine containing foods have been reported in patients taking the recommended daily dose of selegiline. The
   Deletion: the word "and" in the 3rd sentence.

4. PRECAUTION section, Information for Patients subsection:
Addition: 3rd sentence: Rare hypertensive reactions with selegiline at recommended doses associated with dietary influences have been reported.
Deletion: 3rd sentence: While hypertensive reactions with selegiline associated with dietary influences have not been reported, documented experience is limited.

Conclusions:
I recommend that all labeling supplements prior to SLR-003 be acknowledged and retained, and SLR-003 (ELD:R13) should be reviewed by the medical officer and if found acceptable, the labeling supplement should be approved, and that a supplemental NDA acknowledgment/approval letter should issue.

/S/

Teresa Wheelous
Regulatory Management Officer

/S/ 7/16/97

Jack S. Purvis
Supervisory RMO

cc:
Original NDA 20-647
HFD-120/Div. Files
HFD-120/PLeber
HFD-120/RKatz/JSherry
HFD-120/Paul Leber, M.D.
HFD-120/JPurvis/TWheelous

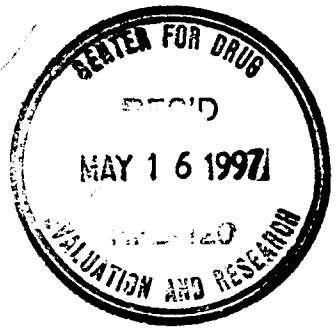
Draft: 7/16/97tw c:\wheelous\eldepryl-cap\20647\label.cso
nda\20647\label.cso
Final:

CSO REVIEW

Somerset
PHARMACEUTICALS, INC.

P.O. Box 30706 • Tampa, Florida 33630-3706 • Telephone: (813) 288-0040

ORIGINAL



May 6, 1997

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

NDA NO. 20-647 REF. NO. SLR-003
NDA SUPPL FOR FPL

Dear Dr. Leber:

RE: NDA# 20,647
Eldepryl® Capsules (selegiline hydrochloride), 5mg.

Enclosed please find 12 copies of revised final printed labeling for the referenced drug product. This labeling provides the changes outlined in the correspondence from FDA dated February 7, 1997.

Very Truly Yours,

Cheryl Blume

5/30/97
NAI
/S/

Cheryl D. Blume, Ph.D.
Executive Vice President

cc: Teresa Wheelous, CSO

ADMINISTRATION
5215 West Laurel Street
Tampa, Florida 33607-1729
Fax: (813) 282-0085

LABORATORY
5415 West Laurel Street
Tampa, Florida 33607-1729
Fax: (813) 288-9442

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FEB - 7 1997

NDA 20-647/S-002
NDA 19-334/S-16

Somerset Pharmaceuticals, Inc.
Attention: Cheryl Blume, Ph.D.
5415 West Laurel Street
Tampa, Florida 33607

Dear Dr. Blume:

Please refer to your new drug applications for Eldepryl (selegiline) 5mg tablets and capsules.

We also refer to your supplements dated December 23, 1996 which provide for labeling changes.

We have recently reviewed the package insert dated December 23, 1996 and request that, in addition to the revisions incorporated in your outstanding labeling supplements (NDA 20-647/S-002 and NDA 19-344/S-016) that the following changes to the CLINICAL PHARMACOLOGY section of labeling be made so as to furnish adequate information for the safe and effective use of the drug:

1. The fifth paragraph, second sentence should be changed from:
" However, one case of hypertensive crisis has been reported in a patient taking the recommended dose of selegiline and a sympathomimetic medication (ephedrine). "

To:

Although rare, a few reports of hypertensive reactions have occurred in patients receiving Eldepryl® at the recommended dose, with tyramine containing foods. In addition, one case of hypertensive crisis has been reported in a patient taking the recommended dose of selegiline and a sympathomimetic medication, ephedrine.

2. The sixth paragraph should be changed from:

In short, attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use although, as noted above, a case of hypertensive crisis has been reported at the recommended dose. (See WARNINGS and PRECAUTIONS.)

To:

In short, attention to the dose dependent nature of selegiline's selectivity is critical if it is to be used without elaborate restrictions being placed on diet and concomitant drug use although, as noted above, a few cases of hypertensive reactions have been reported at the recommended dose. (See WARNINGS and PRECAUTIONS.)

Please submit final printed labeling exactly as specified above in the form of a SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED as described under 21 CFR 314.70(c). To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit sixteen copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material.

If you have any questions, please contact:

Teresa Wheelous, R.Ph.
Regulatory Management Officer
(301) 594-2777

Sincerely yours,

/S/ 2/4/97

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

cc:
Original NDAs 20-647, 19-334
HFD-120/Div. Files /S/ 1/5/97
HFD-120/CSO/TWheelous
HFD-120/RKatz /S/ 2/4/97
HFD-120/JSherry

drafted: tw/January 29, 1997/m:\dos\wpfiles\nda\19334(20667)\slr016(002).ltr
r/d Initials:
final: 2/3/97

SUPPLEMENT REQUEST

APPEARS THIS WAY
ON ORIGINAL

Somerset
PHARMACEUTICALS, INC.

5215 West Laurel Street
Tampa, Florida 33607-1729
(813) 288-0040
FAX (813) 282-0085

ORIGINAL
NDA SUPPLEMENT
NDA No. 20-647 REF. NO. SLR-002
NDA SUPPL FOR Labeling

APPEARS THIS WAY
ON ORIGINAL

December 23, 1996

SPECIAL SUPPLEMENT
CHANGES BEING EFFECTED

CENTER FOR DRUG
REC'D
JAN - 2 1997
HFD-120
EVALUATION AND RESEARCH

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

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Leber:

RE: NDA# 20,647
Eldepryl® Capsules (selegiline hydrochloride), 5mg.

Enclosed please find revised final printed labeling for the referenced drug product. This labeling provides the changes outlined in the facsimile provided to me by Teresa Wheelous, R.Ph. on October 24, 1996. These revisions also respond to FDA's letter dated November 3, 1995 to NDA#19-334 for Eldepryl® Tablets, 5 mg. As directed by you in our teleconference on October 3, 1996, this supplement has been designated "changes being effected".

Thank you for your assistance in this matter.

APPEARS THIS WAY
ON ORIGINAL

Very Truly Yours,

Cheryl Blume

Cheryl D. Blume, Ph.D.
Executive Vice President

cc: Teresa Wheelous, CSO

APPEARS THIS WAY
ON ORIGINAL

Somerset
PHARMACEUTICALS, INC.

P.O. Box 30706 • Tampa, Florida 33630-3706 • Telephone: (813) 288-0040

ORIGINAL

NDA NO. 20-647 REF. NO. SLR-001
NDA SUPPL FOR Labeling (at least)

October 10, 1996

NDA SUPPLEMENT

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

APPEARS THIS WAY
ON ORIGINAL

Dear Dr. Leber:

RE: NDA# 20-647: Supplement 03
Eldepryl® (Selegiline Hydrochloride) Capsules, 5mg.

Reference is made to your letter dated May 15, 1996 and our October 3, 1996 teleconference. Enclosed please find draft labeling revised to reflect the three reported events of hypertensive reactions. Modifications have been made to the applicable portions of the Clinical Pharmacology and Precautions (Drug Interactions) sections. I have also enclosed a Dear Doctor Letter describing these revisions.

Very Truly Yours,

Cheryl Blume

APPEARS THIS WAY
ON ORIGINAL

Cheryl D. Blume, Ph.D.
Executive Vice President and
Chief Operations Officer

CDB:mlg

cc: Teresa Wheelous, CSO

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 11 1996
HFD-120

ADMINISTRATION
5215 West Laurel Street
Tampa, Florida 33607-1729
Fax: (813) 282-0085

LABORATORY
5415 West Laurel Street
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