CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-025

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

LABELING & ADMINISTRATIVE ISSUES

NDA 21-025
Exelon®
(Rivastigmine Tartrate) Oral Solution
2.0 mg/mL
Classification: 1S

Labeling K

Package Insert:

DRAFT:	4/7/98	Original Subm.
FDA Proposed:	5/12/99	A/E ltr to NDA 20-823 Exelon Capsules
ReDRAFT:	10/22/99	Resp. to A/E ltr

Container/Carton Labels:

DRAFT:	4/7/98	Original Subm.
FPL:	3/17/00	

Patent Information L

Exclusivity Checklist M

Pediatric Page Mc

Debarment Certification N

Division of Scientific Investigations Audit of Studies **(FROM NDA 20-823)** O

2/24/98	DSI Letter to Dr. Peter Ripley	VAI2
3/17/98	DSI Letter to Dr. Peter Dal-Bianco	NAI
4/6/98	DSI Letter to Dr. Patricia Walicke	VAI2
5/27/98	DSI Letter to Prof. Marcel Chatel	VAI2
2/26/98	DSI Memo regarding status of inspections, R. Young	
8/16/99		
4/4/2000	DSI Summary Memo, Constance Lewin, M.D.	

Nomenclature Committee **(FROM NDA 20-823)** P

4/10/97	Memo requesting update of Consult# 705 with 6/23/97 Nomenclature Committee response attached
2/28/00	OPDRA Assessment

Application: NDA 21025/000
Stamp: 11-AUG-1998
Regulatory Due: 22-APR-2000
Applicant: NOVARTIS PHARMS
59 RT 10
EAST HANOVER, NJ 079361080
Priority: 1S
Org Code: 120

Action Goal:
District Goal: 12-APR-1999
Brand Name: EXELON(RIVASTIGMINE TARTRATE)2MG/ML ORAL
Estab. Name:
Generic Name: RIVASTIGMINE TARTRATE

Dosage Form: (SOLUTION)
Strength: 2 MG/ML

Application Comment:
FDA Contacts: R. NIGHSWANDER (HFD-120) 301-594-2850 , Project Manager
W. RZESZOTARSKI (HFD-120) 301-594-2850 , Review Chemist
M. GUZEWSKA (HFD-120) 301-594-5571 , Team Leader

Overall Recommendation: ACCEPTABLE on 21-SEP-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1911445
NOVARTIS CONSUMER HEALTH INC
NORTHEAST US 6 AND INTERSTATE 80
LINCOLN, NE 68517

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: LIQ
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-SEP-1998				RZESZOTARS
SUBMITTED TO DO	11-SEP-1998	10D			FERGUSONS
DO RECOMMENDATION	18-SEP-1998			ACCEPTABLE	GDICKINS
THE LAST CGMP INSPECTION OF THIS FIRM WAS CONDUCTED 4/24/98 AND INCLUDED COVERAGE OF THE PROFILE CLASS LIQUIDS. ONLY MINOR DEFICIENCIES WERE NOTED.				BASED ON FILE REVIEW	
OC RECOMMENDATION	21-SEP-1998			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment: 9611204
NOVARTIS PHARMA INC (SANDOZ)
CH-4002
BASEL, , SZ

DMF No:
AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN
OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-SEP-1998				RZESZOTARS
OC RECOMMENDATION	11-SEP-1998			ACCEPTABLE	FERGUSONS

Note to the reviewer:

The text of this draft package insert includes all of the information from the Revised Draft Labeling for EXELON Capsules (NDA 20-823), submitted August 27, 1997 in the Exelon Capsule 120-day Safety Update. That information is printed in regular font. New information relating to EXELON Oral Solution is underlined. Information which does not pertain to EXELON Oral Solution is crossed-out. In addition, a vertical line in the left margin designates where the above described changes to the text have been made.

The final package insert for Exelon Oral Solution will be adapted to the Exelon Capsule labeling upon approval of the Exelon Capsule NDA. We have provided a separate package insert for Exelon Oral Solution for simplicity. However, we would consider a combination package insert for both Exelon Capsules and Oral Solution at a later time.

APPEARS THIS WAY
ON ORIGINAL

NOVARTIS

Robert W. Kowalski, PharmD
Director, Global Head
Planning and Administration
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel (973) 781-6869
Fax (973) 781-4537
Internet robert.kowalski
@pharma.novartis.com

March 17, 2000

Russell Katz, MD
Director
Division of Neuropharmacological
Drug Products/HFD-120
Office of Drug Evaluation I
Attn: Document Control Room
Center for Drug Evaluation and Research
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

NDA No. 21-025

EXELON® (rivastigmine tartrate)
Oral Solution

FINAL PRINTED LABELING

Dear Dr. Katz,

Reference is made to our pending New Drug Application for Exelon® (rivastigmine tartrate) Oral Solution, NDA 21-025, and our Complete Response to an Approvable Action which was submitted on October 22, 1999.

The present submission provides final printed labeling for Exelon Oral Solution. The various presentations of bottle and package labels are as follows:

- 120 mL bottle label; Labeling control number 85025201
- Outer container label (secondary packaging) for the 120 mL bottle: Labeling control number 83015501

The labeling presented herein is identical to the previously submitted draft text labeling with the following noted changes:

- The storage condition has been changed to "Store and dispense upright below 25 degrees C (77 degrees F)"; protect from freezing", per Dr. W. Rzeszotarski of your Division. This change was communicated by Mr. R. Nighswander in a teleconference at the time the approvable action was issued.
- The "Caution" statement has been replaced with Rx Only.
- The "Manufactured by" statement has been updated to be more specific.

If you have any comments or questions with regard to the Chemistry, Manufacturing & Controls information in this submission, please contact Ms. Sheryl LeRoy at (973) 781-2735. For all other inquiries, please contact the undersigned at (973) 781-6869.

Sincerely,

Robert W. Kowalski, Pharm.D.
Director,
Drug Regulatory Affairs

cc: 2 desk copies under separate cover to R. Nighswander (HFD-120)

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 2

❖❖❖

Draft Labeling
(not releasable

Section 13 - PATENT INFORMATION

ENA 713 (Exelon®) and its use in treating senile dementia and Alzhimer's disease are claimed in USP 4,948,807, which expires August 14, 2007.

ENA 713 (Exelon®), pharmaceutical and transdermal compositions containing it and its use in treating senile dementia and Alzheimer's disease are claimed in USP 5,602,176, which expires February 11, 2014.

APPEARS THIS WAY
ON ORIGINAL

Section 14 - PATENT CERTIFICATION

Not applicable.

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-025 SUPPL #_____

Trade Name Exelon® Generic Name Rivastigmine Tartrate Oral Solution 2.0 mg/mL

Applicant Name Novartis Pharmaceuticals Corporation HFD-120

Approval Date, if known 4/21/2000

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA?

   YES /_X_/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X_/

   If yes, what type? (SE1, SE2, etc.) _____

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

   YES /___/ NO /_X_/

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

   _____

   _____

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

   _____

   _____

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

1. Single active ingredient product.

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

YES /___/ NO /_X_/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 9. IF "YES" GO TO PART III.

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

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

_____

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

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

Rx-to-OTC switches should be answered No - please indicate as such.

YES /___/ NO /_X_/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 9.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 9 (even if a study was required for the upgrade).

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

1. Single active ingredient product.

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

YES /___/ NO /_X_/

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

NDA# ____20-823_____ _Exelon Oral Capsules___

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 9. IF "YES" GO TO PART III.

PART III <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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

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

YES /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data,

would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those *conducted* or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s are considered to be bioavailability studies.

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

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 9:**

_____

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

YES /___/ NO /___/

If yes, explain: _____

_____

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

Investigation # 1, Study # _____

Investigation # 2, Study # _____

Investigation # 3, Study # _____

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

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

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

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

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

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

Investigation # ___ Study # _____

Investigation # ___ Study # _____

Investigation # ___ Study # _____

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

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

Investigation #1

IND # _____ YES /___/ ! /NO /___/ Explain: _____

_____

_____

Investigation #2

IND # _____ YES /___/ ! /NO /___/ Explain: _____

_____

_____

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

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

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

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/ 4-27-2000

Signature of Preparer Date

Title: Project Manager

/S/ 4/29/00

Signature of Office or Division Director Date

cc:
Archival NDA
HFD-120/Division File
HFD-093/Mary Ann Holovac
HFD-104/T. Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21025	**Trade Name:**	EXELON(RIVASTIGMINE TARTRATE)2MG/ML ORAL
Supplement Number:		**Generic Name:**	RIVASTIGMINE TARTRATE
Supplement Type:		**Dosage Form:**	SOL
Regulatory Action:	AP	**Proposed Indication:**	Exelon is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Alzheimer's indication.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER. ROBBIN NIGHSWANDER

/S/

Signature

4-20-2000

Date

APPEARS THIS WAY
ON ORIGINAL

Section 16 - DEBARMENT CERTIFICATION

EXELON® (rivastigmine tartrate) 2 mg/ml Oral Solution

New Drug Application

NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENCORCEMENT ACT OF 1992

NOVARTIS PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

August 11, 1998
Date

Robert W. Kowalski, Pharm.D.
Associate Director
Drug Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Peter M.Ripley, M.D.
Clinical Studies
23H White's Path
South Yarmouth, Massacheusetts 02664

FEB 24 1998

Dear Dr. Ripley:

In October and November 1997, Ms. Sandra P. White, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as Principal Investigator, of a clinical study of the investigational drug Exelon (SDZ ENA 713), performed for Sandoz Pharmaceuticals Corporation (now Novartis). This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report, of the documents collected during the inspection, and of your November 10, 1997 letter to Ms Carolanne Currier of our office, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects in the following respects: An investigator is required to prepare and maintain adequate and accurate case histories. 21 CFR 312.62(b). Your case histories should capture observations made during the trial including identification of each subject and each subject's related study documents.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Ms. White during the inspection.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

CFN:
Field classification:VAI
Headquarters classification:
_____1)NAI
_X___2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is different classification, explain why:

Deficiencies noted:
_____ inadequate consent form
_____ inadequate drug accountability
_____ failure to adhere to protocol
_X___ inadequate records
_____ failure to report ADRS _____
_____ other (specify)

cc:
HFA-224
HFD-344
HFD-340
HFR-NE250___
HFR-NE250___
HFD-120 Review Division Div. Dir./Doc. Rm.: NDA#20-823
MO:M.Sevka CSO:L.Chen

r/d:RSKYoung:2/20/98
corrected:slk:2/20/98

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Orig NDA
20-823

MAR 17 1998

Dr. Peter Dal-Bianco
Universitatskliniken fur
Neurologie
Wahringer Gurtel 18-20
A-1090 Wien
AUSTRIA

Dear Dr. Dal-Bianco:

Between December 1-5, 1997, Ms. M. Patricia Murphy and Dr. Robert Young, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as Principal Investigator, of a clinical study of the investigational drug Exelon (SDZ ENA 713), performed for Novartis Pharmaceuticals Corporation (formerly Sandoz Pharma Ltd.). This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

Although your clinical study was conducted under an Investigational New Drug Exemption (IND) held by Novartis and you signed a Form FDA 1572 Statement of Investigator, it was clear in discussions with you during the inspection that you were unaware at the time you signed the Form to what exactly you were committing yourself. From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that there were some departures from pertinent federal (FDA) regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We share these with you for your information should you conduct another study under an IND. As was discussed with you by Ms. Murphy and Dr. Young, FDA has specific rules for example as to the membership of ethic committees, the implementation of protocol amendments, the inventory of study medications, identification of all documents related to a study, and documentation of the initial condition and medical progress of subjects during the course of a study.

We appreciate the cooperation shown Ms. Murphy and Dr. Young during the inspection.

Sincerely yours,

(S)

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

APPEARS THIS WAY
ON ORIGINAL

CFN:
Field classification: AE
Headquarters classification:
_X_ 1) NAI - in compliance with local rules
_____ 2) VAI-no response required
_____ 3) VAI-response requested

If Headquarters classification is different classification, explain why:

cc:
HFA-224
HFD-344
HFD-340
HFR-NE250
HFR-NE250
HFD-120 Review Division Div. Dir./Doc. Rm.: NDA#20-823
MO:Sevka CSO:L.Chen

r/d:RSKY:3/11/98
corrected:slk:3/11/98

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

30.823

APR - 6 1998

Patricia A. Walicke, M.D., Ph.D.
Athena Neurosciences
800 Gateway Boulevard
South San Francisco, California 94080

Dear Dr. Walicke:

On September 2-17, 1997, Ms. Stephanie E. Hubbard, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as Principal Investigator, of a clinical study of the investigational drug Exelon (SDZ ENA 713), performed for Sandoz Pharmaceuticals Corporation (now Novartis). This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report, of the documents collected during the inspection, a September 23, 1997 letter from Mr. Michael Jann to Ms. Hubbard, and your March 26, 1998 conversation with Dr. Robert Young of our office, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects in the following respects:

> An investigator is required to ensure that the requirements relating to obtaining informed consent and institutional review board review and approval are met. 21 CFR 312.53(c)(1)(vi)(d). You should submit recruitment advertisements to your IRB for their review and approval. You should obtain timely IRB approval of protocol amendments and revise your written informed consent document as appropriate. You should report serious adverse reactions to your IRB in a timely manner.

We note that your study was conducted at two separate sites and was reviewed by two different IRBs. There appeared to be some difficulty in the administration of the study.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Ms. Hubbard during the inspection.

Sincerely yours,

/S/

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation and
Research

cc:
Michael Jann, PharmD
Mercer University
3001 Mercer University Drive
Atlanta, GA 30341

APPEARS THIS WAY
ON ORIGINAL

cc:
HFA-224
HFD-120 Review Division Div. Dir./Doc. Rm.: NDA#20-823
HFD-120 MO:
HFD-120 PM:
HFD-340/R/F
HFD-344
HFR-SE150 DIB
HFR-SE150 BIMO Monitor
HFR-SE150 Field Investigator Hubbard

CFN:
Field classification: not classified
Headquarters classification:
_____1)NAI
_X___2)VAI-no response required
_____3)VAI-response requested
_____4)OAI

If Headquarters classification is different classification, explain why:

Deficiencies noted:
_____ inadequate consent form
_____ inadequate drug accountability
_____ failure to adhere to protocol
_____ inadequate records
_X___ failure to report ADRS _____
_X___ Failure to obtain timely IRB review of amendments, and consents

r/d:RSKY:3/26/98
corrected:slk:3/31/98

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 27 1998

Prof. Marcel Chatel
Hospital Pasteur
30 Avenue de la Voie Romaine
F-06002 Nice Cedex 1
FRANCE

Dear Prof. Chatel:

On November 6-10, 1997, Doctors Gerald N. McGirl and Robert Young, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as Principal Investigator, of a clinical study of the investigational drug Exelon (SDZ ENA 713), performed for Novartis. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you did not adhere to pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects in the following respects:

1. Consent forms should cover all of the elements required by 21 CFR 50.25(a), which is enclosed.

2. Observations required by the protocol such as respiratory rate, blood pressures, etc. should be made.

3. All study related papers should be identified so that it is clear to which subject they belong.

4. Hospital notes should capture a subject's clinical course.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown our personnel during the inspection.

Sincerely yours,

/S/

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific
Investigations
Office of Compliance
Center for Drug Evaluation
and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
HFA-224
HFD-120 Review Division Div. Dir./Doc. Rm.: NDA#20-823
HFD-120 MO:
HFD-120 PM:
HFD-340/R/F
HFD-344
HFR-PA150 DIB
HFR-PA150 BIMO Monitor

CFN:
Field classification: NAI
Headquarters classification:
_____1) NAI
__X__2) VAI-no response required
_____3) VAI-response requested
_____4) OAI

If Headquarters classification is different classification, explain why: some deficiencies

Deficiencies noted:
__X__ inadequate consent form
_____ inadequate drug accountability
__X__ failure to adhere to protocol
__X__ inadequate records
_____ failure to report ADRS _____
_____ other (specify)

r/d:RSKY:5/19/98
finaled:slk:5/20/98

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

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

DATE: February 26, 1998

FROM: Robert Young
HFD-344

TO: Robbin Nighswander
HFD-120

SUBJECT: NDA 20-823: Novartis' Exelon - Clinical Investigator Inspections

The clinical investigators listed below were assigned for inspection and have been inspected. Nothing was found in the course of the inspections which would preclude use of the data they submitted in support of an approval of NDA 20-823.

Marcel Chatel	Nice
Peter Dal-Bianco	Vienna
Michael Jann	Atlanta
Peter Ripley	South Yarmouth

Robert S. K./Young

DEPARTMENT OF HEALTH & HUMAN SERVICES

20-823

Food and Drug Administration
Rockville MD 20857

AUG 16 1999

Dear Dr. .

Between January 5 and 13, 1999, Ms. Stephanie Hubbard, Mr. Allen Hall, and Dr. Robert Young, representing the Food and Drug Administration (FDA) conducted an inspection of monitoring by , of Protocols B351 and ENAB 355-E-00 (Sandoz Pharmaceutical Corp.), and Protocol D92-026 c.). This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based, and to assure that the rights and welfare of the human subjects of those studies have been protected by appropriate monitoring of those clinical studies. At the conclusion of the inspection, Ms. Hubbard, Mr. Hall and Dr. Young issued to you a Form FDA 483 and discussed the inspectional findings with you, Jack Van Loon, Ann Humphreys, Linda Patterson, Cassandra Kennedy, Barbara Finn, and Roger Thies.

From our evaluation of the inspection report, the documents collected during the inspection, and your March 3, 1999, letter (with attachments) to Ms. Hubbard, Mr. Hall and Dr. Young, we conclude that you failed to ensure proper monitoring (21 CFR sections 312.50 and 312.52) in the following areas:

1. Failure to close monitoring visit reports in a timely manner. You repeatedly failed to either write, or review, and approve monitoring visit reports in a timely manner. In many instances monitoring visit reports were not either written soon after a monitoring visit, or written, but not reviewed and approved by a supervisor/manager at all, or for several months after the site visit monitoring report (itself) had been finalized by its author. Although FDA regulations do not specifically state that a monitoring visit report is complete and final only after two persons agree on its contents, the agency does subscribe to in (and practice in) more complex situations a two heads is better than one approach. The primary objective of the monitoring of an on going study is to promptly identify and correct problems and deficiencies which might imperil subjects and/or a study. Timely completion of site visit monitoring reports is an essential part in achieving this monitoring objective.

Your procedures, furthermore, required that review and approval be completed before monitoring visits reports became part of a protocol's study file. In these multicenter studies your failure to complete monitoring reports meant that an overall picture of how a study was progressing was

incomplete for months. Examples include, from Protocol B351 several examples of final site visit reports showing no review/approval; from Protocol B355 a site visit report completed on February 27, 1997, and reviewed/approved on May 27, 1997; and from Protocol 26 a report of a May 22, 1998, monitoring visit that was reviewed and approved on August 15, 1998.

2. Failure to follow your standard operating procedures [SOP(s)] on handling suspected scientific misconduct and/or possible fraud in clinical trials. A monitor for a Protocol B355 study site, through astute observation of study site procedures, personnel, and activities during his visits, related questionable activities at the site in his monitoring reports and separately to his supervisors. For example, he reported forged principle investigator signatures, questionable delegations of authority of study tasks to incompetent employees, possible overreaching in securing a study subject's continued participation in a study, etc.

The position that you took at the time was that the questionable activities reported by your monitor were not worth believing. Although we realize that it is not always easy to ferret out what exactly is going on during the conduct of a study, in spite of repeated demands by your monitor for follow up action, we found no documentation in support of your position. Additionally, we found no documentation of steps you took to further investigate the complained of situation be it to verify the credibility of your monitor, or activities at the site, replace the monitor, etc. In fact the record seems to suggest that this employee was actually hounded out of your organization for merely persisting in his line of questioning.

We understand that stricter procedures were instituted after and independent of the above events. We further understand that even tighter procedures were put into place as a result of the above events. Your March 3, 1999, letter is accepted as your assurance that corrective actions have been taken to prevent similar problems as are described above. Your letter has been added to your file. If information is requested from your file that relates to your letter, in accord with the Freedom of Information Act, our response includes related correspondence (except for appendices) in your file.

Although we encourage your efforts to date, we are troubled nonetheless by a perceived lack of commitment on your part to putting the research subject and research data first. Although we did not discuss the following matter with you as you had no direct control over it, we had received from [redacted], your parent, copies of drafts and a final report of a Quality Assurance (QA) visit to this same Protocol B355 site. In fact you personally initiated this quality assurance audit, received and reviewed the report, and forcefully recommended commensurate action. This team verified most of the suspected misconduct reported by the monitor. This team's report was as you may know subjected, however, to "legal" review, something we were told is not routinely done at [redacted] There was an attempt to limit inclusion in the report of only those QA findings that met a kind of beyond a reasonable doubt test. Measured against this standard, few if any QA or monitoring findings would ever make it into reports. So long as the limitations that constrain reported findings are clear, it should be for the reader to credit the weight and import of findings.

We shall closely monitor your clinical trial monitoring practices in order to ensure that you have indeed implemented safeguards such as your revised procedures including employee training and to gauge the progress you have made to increase your sensitivity for uncovering misconduct and addressing allegations of misconduct at noncompliant sites.

We appreciate the assistance given during the inspection.

Sincerely,

/S/

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practices II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

cc:
Mr. Dennis Gillings
Chairman

APPEARS THIS WAY
ON ORIGINAL

CFN:
Field Classification: OAI
Headquarters Classification:
___1) NAI
___2) VAI-no response required
_X_3)VAI-response received, evaluated

If Headquarters classification is different classification, explain why:
Corrective action has been implemented and assurances accepted.

Deficiencies noted:
___1-Failure to establish adequacy of laboratory facilities
used by the clinical investigator
___2-Failure to maintain adequate records of drug accountability
___3-Absence of Standard Operating Policy
___4-Failure to review patient records
___5-Failure to assure IRB approval
___6-Failure to document monitoring visits
___7-Failure to visit study site before and during study
_X_8-Other: **Inadequate monitoring of clinical trials**

cc:
HFA-224
HFD-120:Division Director
HFD-120:Doc Room: NDA 20-823, NDA 21-025, ———
HFD-45 r/f
HFD-47 c/r/s GCP file#2172
HFD-47/Young
HFR-SE150/Kline
HFR-SE150/BiMo-Todd
HFR-SE150/Hubbard
HFR-PA2565/BiMo-Koller
HFR-PA250/Kozick
HFR-PA250/A. Hall

APPEARS THIS WAY ON ORIGINAL

r/d:Young:
reviewd: AEH:
f/t:nlp:8/13/99

COMPLETED APR 10 2000

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: April 4, 2000

TO: Robbin Nighswander, R. Ph., Regulatory Project Manager
Ranjit Mani, M.D., Clinical Reviewer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDAs: 20-823 (capsules) & 21-025 (liquid)

APPLICANT: Novartis Pharmaceuticals

DRUG: Exelon (rivastigmine tartrate)

CHEMICAL CLASSIFICATION: 1

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of mild to moderate dementia of the Alzheimer's type (NDA 20-823)
Treatment of Alzheimer's Disease (NDA 21-025)

CONSULTATION REQUEST DATE:

ACTION GOAL DATES: April 21, 2000 (NDA 20-823)
April 22, 2000 (NDA 21-025)

I. BACKGROUND:

Routine and directed clinical inspections were conducted in conjunction with the above-noted applications. Inspection results are noted below.

APPEARS THIS WAY
ON ORIGINAL

II. RESULTS (by protocol/site):

Name	City	State	Country	Assigned Date	Received Date	Classification
Chatel	Nice	--	France	10-22-97	04-22-98	VAI
Dal-Bianco	Vienna	--	Austria	10-29-97	02-05-98	NAI
Ripley	S. Yarmouth	MA	USA	06-26-97	12-09-97	VAI
Walicke/Jann	Atlanta	GA	USA	06-26-97	03-02-98	VAI
Potkin	Orange	CA	USA	07-27-99	Pending	Pending review
Nakra	St. Louis	MO	USA	08-04-99	Not done – See explanation below	

A. Protocol ENA B303

1. Site #1 (Chatel – Nice, France):

   Twenty-nine (29) subjects were enrolled in this study at this site. This was a routine data audit, in which records from ten (10) subjects were reviewed. No Form FDA 483 was issued. However, in an information letter, the principal investigator was informed of findings regarding informed-consent inadequacies and inadequate recordkeeping.

   Data appear acceptable.

2. Site #2 (Dal-Bianco – Vienna, Austria):

   Thirty (30) subjects were enrolled in this study at this site. This was a routine data audit, in which records for eight (8) subjects were reviewed. No Form FDA 483 was issued. However, in an information letter, the principal investigator was informed of findings regarding protocol deviations and inadequate recordkeeping.

   Data appear acceptable.

B. Protocol ENA B352

1. Site #1 (Ripley – South Yarmouth, MA)

   Forty-six (46) subjects were enrolled in this study at this site. This was a routine data audit, in which twenty percent of subject records were reviewed. A Form FDA 483 was issued. In an information letter, the principal investigator was informed of findings regarding inadequate recordkeeping.

   Data appear acceptable.

2. Site #2 (Walicke/Jann – Atlanta, GA)

   Thirty-five (35) subjects were enrolled in this study at two sites in Atlanta, Georgia. Dr. Walicke was the original principal investigator; Dr. Jann subsequently took over those responsibilities. This was a routine data audit, in which records for six (6) subjects were reviewed. A Form FDA 483 was issued. In an information letter, Drs. Walicke and Jann were informed of findings regarding inadequate recordkeeping, failure to submit advertisement materials for IRB approval, failure to obtain IRB approval of protocol amendments in a timely fashion, and failure to report serious adverse events to the IRB in a timely fashion.

   Data appear acceptable.

C. **Protocols ENA B-351 & B-353**

Site #1 (Potkin – Orange, CA):

This directed inspection was issued based upon a complaint that a subject (#111-49) may have died of pancreatitis, possibly related to study drug, and that an unlicensed physician signed his name to study records for Dr. Potkin. This inspection is presently ongoing, so there is no establishment inspection report yet.

Based upon limited information obtained from the field investigator, no significant information was gathered to substantiate the allegations. Accordingly, there appear to be no findings that would preclude the acceptability of data generated at this site.

D. **Protocol ENA B-356**

Site #1 (Nakra – St. Louis, MO):

According to the field office, this directed clinical inspection was never conducted because of an investigation by Office of Criminal Investigations (OCI) that was initiated shortly after, and apart from, the issuance of the assignment relating to this study. The OCI case is currently ongoing. As clinical inspection was precluded by OCI involvement at this site, we are unable to advise regarding the acceptability of data generated at this site.

APPEARS THIS WAY
ON ORIGINAL

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As noted above, we are unable to make a recommendation regarding the acceptability of the data generated at Dr. Nakra's site for protocol ENA B-356 because the directed inspection that would have covered this study was never initiated. The data from all other sites included in this inspection summary appear acceptable for use in support of the pending application. However, we wish to emphasize that the establishment inspection report (EIR) on Dr. Potkin has not yet been received. Therefore, as stated previously, the recommendation regarding acceptability of data from this site is based on limited information from the field. Should the EIR contain additional information that would change our recommendation regarding Dr. Potkin's data, you will be so informed.

/S/

Constance Lewin, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

/S/

Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

DISTRIBUTION:
NDA 20-823
NDA 21-025
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/Lewin/Hajarian
HFD-47/GCP II Branch Chief
HFD-47/Kline for GCPB File #####
HFD-47/Reading File

APPEARS THIS WAY
ON ORIGINAL

Re Submission

Consult 705

OUTGOING

APR 11 1997

MEMORANDUM

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

DATE: April 10, 1997

/S/

FROM: Paul Leber, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Request for Assessment of a Trademark for a Proposed Drug Product

TO: Dan Boring, Chair
Labeling and Nomenclature Committee
HFD-530, Corporate N461

RETURN

1997

Proposed Trademark: **Exelon™ NDA # 20-823**

Established name, including dosage form:

[redacted] **[NOTE: This name has not been approved by either USAN or WHO. The firm is awaiting final approval and expects to hear within 1 - 2 months]**

Other trademarks by the same firm for companion products: **None**

Indications for Use (may be a summary if proposed statement is lengthy):

Exelon™ is indicated for the treatment of mild to moderately severe dementia of the Alzheimer's type.

Initial comments from the submitter: (concerns, observations, etc.)

Please note that this proposed Tradename has been previously reviewed by the committee under the IND [redacted] Copy attached.

cc:
ORIG NDA
HFD-120
HFD-120/SBlum/Rzeszotarski
HFD-120/RNighswander
n20823.nam

4

RETURN

Consult ——— Resubmission)

1997

EXELON

This is a resubmission of a proprietary name that was evaluated at the IND stage. The product has now reached the NDA stage. There are still no look-alike/sound-alike conflicts or misleading aspects found in the proposed proprietary name.

The Committee has no reason to find the proposed proprietary name unacceptable.

S

_____, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

RETURN

Consult _____ 1997

EXELON

SDZ ENA 713 capsules

The Committee is concerned that the prefix EXEL- suggests excellent and there is some potential for promotional misuse with the proposed name. Additionally, the Committee found one look-alike/sound-alike conflict: ENLON, an injectable skeletal muscle relaxant. However, the Committee feels there is a low potential for confusion.

The USAN name is still pending therefore the comments of the Committee are preliminary pending final adoption of the proposed USAN name. Overall, the Committee finds the name acceptable and requests the name to be resubmitted when the product reaches the NDA stage.

/S/

_____, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

COMPLETED MAR 2 8 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 2/3/00	DUE DATE: 3/30/00	OPDRA CONSULT #: 00-0052

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

THROUGH: R. Nighswander, Project Manager, DNDP
HFD-120

PRODUCT NAME: **Exelon®** (rivastigmine), capsules and solution NDA #: 21-025, 20-823	MANUFACTURER: Novartis Pharmaceuticals Corporation.
Safety Evaluator: Peter Tam, RPh.	

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of the proprietary name Exelon®.

/S/ 3/23/2000
Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ 3/23/00
Peter Honig, MD
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

APPEARS THIS WAY
ON ORIGINAL

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

Date of Review: 3/14/00

NDA#: 20-823
21-025

Name of Drug: Exelon®
(rivastigmine), capsules and solution

NDA Holder: Novartis Pharmaceuticals Corporation.

I. INTRODUCTION

This consult was written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) on February 3, 2000, to review the proposed proprietary drug name, Exelon® in regard to potential name confusion with existing proprietary/generic drug names.

——— ., a sponsor for Aricept® and copromoter with Pfizer Inc., filed a complaint with the DDMAC on 10/2/1998 about the proposed trade name of Exelon® ——— felt that the proposed proprietary name Exelon® is false and misleading. A study, sponsored by ——— , had been undertaken by ——— ———— ., which specializes in healthcare marketing. For this study. ——— ——— conducted telephone interviews of 100 randomly selected physicians. They were asked about their awareness of other Alzheimer's therapies, their perceptions of the proprietary name "Exelon®. Survey results demonstrate that proposed name "Exelon" implies a claim of excellence and superiority. claims that the use (if approved) of such a name in product lebeling or advertising would be false and misleading and would misbrand the drug in violation of the Act (21 CFR 201-10(c)(3) and 202.1(a)(3).

The Labeling and Nomenclature Committee (LNC) had reviewed this proprietary name on 1/7/97 when it was filed under IND application. LNC found the name acceptable. However, the committee was concerned that the prefix "EXEL" suggested excellent and there was some potential for promotional misuse with the proposed name. LNC requested the name to be resubmitted when the product reached the NDA stage. When this proposed name, Exelon® was resubmitted for evaluation by LNC on 6/23/97 (NDA stage), LNC found the proposed proprietary

name acceptable. There were still no look-alike and sound-alike names found.

PRODUCT FORMATION

Exelon® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. It is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. It is also rapidly and extensively metabolized primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. Half-life in plasma is approximately 1.6 hours. The major pathway of elimination is via the kidneys.

Rivastigmine exhibits linear kinetics over the dosing range of 1-3 mg bid. At higher doses of 3-6 mg bid, it tends to display nonlinear kinetics; doubling the dose from 3 to 6 mg bid results in a 3-fold increase in AUC (area under the curve). There is no accumulation of rivastigmine in Alzheimer's patients and steady state is reached within 1 day of dosing.

The recommended starting dose of Exelon® is 1.5 mg twice a day. If this dose is well tolerated, after a minimum of two weeks of treatment, the dose may be increased to 3 mg twice a day. The maximum dose is 6 mg bid (12 mg/day).

Exelon® will be supplied as 1.5 mg, 3 mg, 4.5 mg and 6 mg of capsule in bottles of 60, 500 and unit dose package of 100. Oral solution will be supplied as 2 mg/ml in bottle of 120 ml.

II. RISK ASSESSMENT

In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, Exelon® with other drug names, the medication error staff of OPDRA searched Micromedex online, PDR (1999 Edition), American Drug Index (43rd Edition), Drug Facts and Comparisons (update monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. In addition, OPDRA also searched several FDA databases for potential sound-alike and look-alike names to approved/unapproved drug products through DPR, Medline, Decision Support System (DSS), Establishment Evaluation System, and LNC database. An expert panel discussion was conducted to review all the findings from the searches. OPDRA also conducted studies of written and verbal analysis of the proposed proprietary name employing healthcare practitioners within FDA to evaluate potential errors in handwriting and verbal communication of the name. This exercise was conducted to simulate the prescription order process.

A. EXPERT PANEL DISCUSSION:

The expert panel consists of members of OPDRA medication error safety evaluator staff and a representative from the Division of Drug Marketing, Advertising and Communication.

The panel discussion was conducted on 2/22/00. There were no problems found with other similar sounding or looking proprietary drug product names. However, DDMAC expressed concerns about the prefix "exel" portion of the name which might indicate greater efficacy and is promotional.

B. STUDY CONDUCTED BY OPDRA

Methodology:

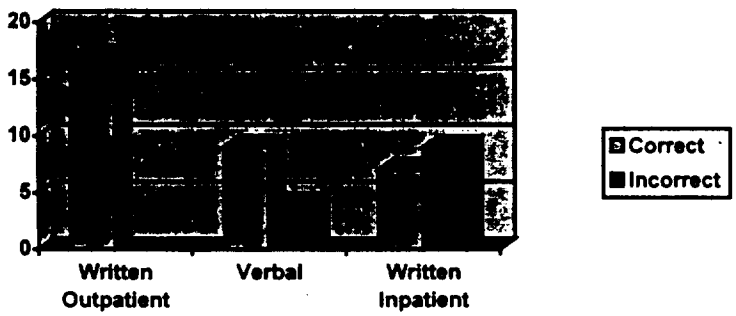
This study involved 92 health professionals consisting of physicians, nurses and pharmacists within FDA to determine the degree of confusion of Combidex® with other drug names due to the similarity in handwriting and verbal pronunciation of the name. An OPDRA staff member wrote three outpatient prescriptions, one consisting of a known drug product, one is for Exelon® and the other one is unknown (unapproved) name. These prescriptions were scanned into the computer and a random sample of the written orders were then delivered to the participating healthcare professionals via e-mail. In addition, four inpatient prescriptions were written, one consisting of a known drug, one is for Exelon® and the other two are unknown (unapproved) proprietary names. Written inpatient and outpatient prescriptions were sent to 31 participants each for review. In addition, one medication error staff recorded the inpatient orders on voice mail. The voice mail messages were then sent to 30 participating healthcare professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff. We recognize that our sample size is small and the study is designed to increase the likelihood of detecting failures.

APPEARS THIS WAY
ON ORIGINAL

The results are summarized in Table I.

Table I

Study	# of Samples	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	31	17 (55%)	17	0
Verbal	30	13 (43%)	9	4
Written Inpatient	31	16 (52%)	7	9
Total	92	46 (50%)	33	13



Seventy-two percent of the participants responded with the correct name Exelon®. The incorrect written and verbal responses are as follows in Table II.

Table II

	Incorrectly Interpret
Inpatient Written	(5)
	2)
	en
	Excedrin*
Verbal	Phonetic Variable Responses

* Currently marketed proprietary name

C. CONTAINER LABEL, CARTON AND INSERT LABELING:

1. Current USP nomenclature standards, under General Notices, recommend that the strength of a drug product is expressed on the container label in terms of milligrams or micrograms or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

   In this case, we believe it is less confusing and allows greater utilization of container label space as shown below:

   Exelon®
   (rivastigmine capsules)
   1.5 mg

   The Description section of the package insert should state:

   "Each capsule, for oral administration, contains rivastigmine tartrate equivalent to 1.5 mg rivastigmine."

2. In accordance with the USP, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g. express as 4 mg (not as 4.0 mg). Therefore, we recommend revising the appropriate strengths of Exelon, 3.0 mg and 6.0 mg to 3 mg and 6 mg accordingly.

3. We also recommend that net contents (e.g. 14, 28, 60, 100, 500 capsules) be moved so not to appear in direct conjunction with the strength.

D. CONCLUSIONS:

Results of the verbal and written analysis studies show 33 participants interpreted proprietary name Exelon® correctly. However, the were 13 inaccurate interpretations in written and verbal pronunciation. There was one interpretation that overlapped with an existing approved drug product, Excedrin, in our written inpatient prescription study. This was not what we predicted in the expert panel discussion, and is a significant finding in a study with a small sample size. However, to put Exelon® in its clinical perspective, several factors have to be considered such as to how and when the drug will be used and what

kind of patient population that will use this drug.

First, Exelon® is a capsule formulation and is available in the following strengths 1.5 mg, 3 mg, 4.5 mg and 6 mg. It is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. The recommended starting dose of Exelon® is from 1.5 mg to 3 mg bid. Excedrin is an OTC tablet product mostly used for minor pains and is dosed on as needed basis. Second, when the sound-alike and look-alike name such as Excedrin is ordered verbally or in written order in an inpatient setting for the treatment of Alzheimer, it will be highly unlikely that Excedrin misinterpreted for Exelon® will be dispensed without seeking clarification on dosing and strength by the dispensing pharmacists. Furthermore, since there is no overlapping administration dosing schedule and strength between Exelon ® and Excedrin, the potential safety risks for confusion is hence decreased.

Finally, the studies and searches conducted within FDA did not reveal any other existing drug names that would render the proposed proprietary name, Exelon® objectionable.

III. RECOMMENDATIONS

A. OPDRA has no objections to the use of the proprietary name Exelon®.

B. DDMAC has no objections to the use of the term "EXEL" for this proprietary name Exelon®.

C. OPDRA recommends the above labeling revisions to encourage the safest possible use of this product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241.

/S/

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur

/S/ 12/3/2000

Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

C.C.

NDA 20-823 & 21-025
Office File
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