CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-083

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**			
TO *(Division/Office)*: HFD-705/Division of Biometrics VI; Attention: Karl Lin, Ph.D.			FROM: HFD-120/Division of Neurology	
DATE: October 25, 2006	IND NO.:	NDA NO.: NDA 22-083	TYPE OF DOCUMENT: *New NDA-Request for Statistical review of Dermal Carcinogenicity Study*	DATE OF DOCUMENT:
NAME OF DRUG: Exelon Transdermal Patch	PRIORITY CONSIDERATION: Standard		CLASSIFICATION OF DRUG: Alzheimer's Disease	DESIRED COMPLETION DATE: June 1, 2007
NAME OF FIRM: Novartis				

COMMENTS/SPECIAL INSTRUCTIONS:

This is a new formulation NDA containing a dermal carcinogenicity study. We are requesting a statistical review and evaluation of the data sets derived from this study. The data sets can be located under N22-083 in the EDR (within the CRT folder and the dataset subfolder).

The nonclinical reviewer for this NDA is David Hawver.

SIGNATURE OF REQUESTER: Melina Griffis (301-796-1078)	METHOD OF DELIVERY (Check one): MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Melina Griffis
10/25/2006 10:55:16 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**			
TO *(Division/Office)*: HFD-410/DSRCS Attention: Jeanine Best; WO#22 Rm4472			FROM: HFD-120;Neurology	
DATE: Oct 25, 2006	IND NO.:	NDA NO.: 22-083	TYPE OF DOCUMENT : New NDA- Patient Package Insert	DATE OF DOCUMENT:
NAME OF DRUG: Exelon Transdermal Patch	PRIORITY CONSIDERATION: User Fee due date 7/8/07		CLASSIFICATION OF DRUG: Alzheimer's Disease	DESIRED COMPLETION DATE: May 1, 2007
NAME OF FIRM: Novartis				

COMMENTS/SPECIAL INSTRUCTIONS:

Please review patient information sheet submitted with NDA 22-083 and provide any feedback by May 1, 2007

The electronic link to the complete application including labeling is in the EDR.

SIGNATURE OF REQUESTER: Melina Griffis (301-796-1078)	METHOD OF DELIVERY (Check one): MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Melina Griffis
10/25/2006 04:01:54 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**			
TO *(Division/Office)*: HFD-420/Director, Division of Medication Errors and Technical Support			FROM: HFD-120/Division of Neurology Products	
DATE: October 25, 2006	IND NO.:	NDA NO.: NDA 22-083	TYPE OF DOCUMENT: New NDA- Name Review Request	DATE OF DOCUMENT: September 8, 2006
NAME OF DRUG: Exelon Patch Transdermal System	PRIORITY CONSIDERATION: User fee due date is 7/8/07		CLASSIFICATION OF DRUG: Alzheimer's Disease	DESIRED COMPLETION DATE: May 1 ,2007
NAME OF FIRM: Novartis Pharmaceuticals				

COMMENTS/SPECIAL INSTRUCTIONS:

Proposed Proprietary Name: Exelon Patch Transdermal System

Trademark registration status/Countries registered(if known): Registered but country unknown

Other proprietary names by same firm for companion products: Exelon Capsules and Oral Solution

United States Adopted Name, dosage form, strength and dosing schedule:
Rivastigmine, patch, 5, 10, [redacted] mg, QD

Indication for use:

Exelon® Patch (rivastigmine) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

Exelon® Patch (rivastigmine) is indicated for the treatment of mild to moderate dementia associated with Parkinson's disease.

Carton & container labeling as well as the proposed PI can be located in the EDR

SIGNATURE OF REQUESTER: Melina Griffis (301-796-1078)	METHOD OF DELIVERY (Check one): MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Melina Griffis
10/25/2006 04:22:38 PM

DSI CONSULT: Request for Clinical Inspections

Date: October 18, 2007

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

cc: Joseph Salewski, , Acting Director, DSI, HFD-45
Russell Katz, MD, Director, HFD-120

From: Melina Griffis, R. Ph, Senior Regulatory Project Manager, HFD-120
Division of Neurology

Subject: **Request for Clinical Site Inspections**
NDA 22-083
Novartis Pharmaceuticals Corporation
Exelon Patch (rivastigmine) Transdermal System

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Prof. Nikolai Yakhno Moscow Medical Academy- Neurology Clinic Department for Neurology and Neurosurgery 11 Rossolimo Street 121019 Moscow RUSSIA	2320	38	Treatment of mild to moderate dementia of the Alzheimer's Type
Prof Andrzej Potemkowski Poradnia Diagnostyki i Leczenia Zaburzen Pamieci Pocztowa 41a 70-356 Szczecin Poland	2320	41	Treatment of mild to moderate dementia of the Alzheimer's Type

International Inspections:

We have requested inspections because (please check all that apply):

__X__ There are insufficient domestic data

____ Only foreign data are submitted to support an application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) June 8, 2007. We intend to issue an action letter on this application by (division action goal date) July 8, 2007. The PDUFA due date for this application is July 8, 2007

Should you require any additional information, please contact Melina Griffis at 301-796-1078.

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/s/

Russell Katz
10/18/2006 04:49:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-083

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
Attention: Martina Struck, PhD
Senior Associate Director
Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Struck:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Exelon Patch (rivastigmine) transdermal system
Review Priority Classification:	Standard (S)
Date of Application:	September 8, 2006
Date of Receipt:	September 8, 2006
Our Reference Number:	NDA 22-083

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 7, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 8, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, call Melina Griffis, RPh, Senior Regulatory Project Manager, at (301) 796-1078.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, RPh, MS
Supervisory Regulatory Project Manager
Division of Neurology Products
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Robbin Nighswander
9/27/2006 04:49:28 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 26, 2007
To:	Russell Katz, MD Director, Division of Neurology Products HFD-120
Thru:	Carol Holquist, RPh Director, Division of Medication Errors and Technical Support HFD-420
From:	Kellie Taylor, PharmD, MPH Safety Evaluator Division of Medication Errors and Technical Support
Subject:	Review of Exelon Patch Labels and Educational Materials
Drug Name(s):	Exelon Patch
Application Type/Number:	NDA 22-083
Applicant/sponsor: Novartis	Novartis
OSE RCM #:	2007-1452

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

1 INTRODUCTION

DMETS reviewed the proposed proprietary name, Exelon Patch, and labels and labeling of the product in OSE Review 2007-532 & 2006-704 (dated May 24, 2007). DMETS did not object to the use of the proposed proprietary name, Exelon Patch, but did identify several areas of risk that could lead to medication errors with the proposed Exelon Patch product. In particular, DMETS had concern with the Sponsor's proposal to express of strength in cm^2, and the potential for confusion and error with the currently marketed oral Exelon capsules and the proposed transdermal Exelon Patch. DMETS also identified areas within the proposed label and labeling that could be improved on to reduce the risk of medication errors and outlined a number of modifications. These concerns were relayed to the Sponsor by the Division of Neurology Products, and subsequently the Sponsor submitted on June 12th modifications in response to DMETS comments. Because these modifications did not fully address the original safety concerns, DMETS and DNP agreed to have a teleconference with the Sponsor on June 15th to resolve the remaining areas of concern. On June 18th, 20th ,and 22nd, the Sponsor submitted meeting minutes from the teleconference, modified labels, and education plans for the proposed product. This memo is in response to the Division's request to review the aforementioned materials, which are listed below in section 2.

2 MATERIAL REVIEWED

The following materials were reviewed by DMETS, and are organized by date of submission.

1. June 15th teleconference minutes. Word document emailed June 18th, 2007 to the Project Manager, DNP.
2. Revised labels for the 4.6 mg/24 hour and 9.5 mg/24 hour Exelon Patch, emailed June 18th, 2007 as PDF documents emailed to the Project Manager DNP; including:
    - graphics of the transdermal system
    - pouch labels
    - carton labels
3. Sponsor's Physician/Patient Education Plan Overview. PDF emailed June 20th, 2007 to the Project Manager, DNP and Safety Evaluator, DMETS.
4. Sponsor's Patient Communication Plan Overview. Microsoft PowerPoint file emailed June 22nd, 2007 to the Project Manager, DNP.
5. Sponsor's Proposal for use of current stock Exelon Patches. PDF document emailed June 22nd, 2007 to the Project Manager, DNP.

3 DISCUSSION

After reviewing the materials submitted June 18th, 20th, and 22nd from a medication errors perspective, DMETS has the identified the following areas of concern.

3.1 CARTON LABELING

Refer to pages 3 and 4 of the teleconference minutes submitted June 18th which state:

Carton

1) Pharmacy label:

Discussion

FDA noted our proposed carton modification to allow for pharmacy label, however was not in agreement with the placement as it would obscure the bar code after dispensing. Dr Katz requested repositioning to preclude obscuring all text.

Agreement

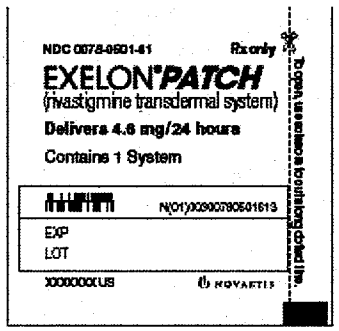
Novartis will modify the carton design to accommodate a pharmacy-generated patient label that will not obscure any text. The pharmacy label area will be repositioned.

DMETS would like to point out that FDA noted that the original positioning of the designated space to affix the pharmacy label would obscure the barcode, which is used to verify the medication during the dispensing process, not after dispensing.

Additionally, it was understood by DMETS from the discussion at the teleconference that Novartis would attempt to relocate the barcode to another panel, rather than relocate the pharmacy label area. DMETS believes that the proposed repositioning of the pharmacy label to the primary display panel avoids the barcode scanning issue but limits the space to display critical information (namely the proprietary name, established name, dosage form, strength, NDC number, and package quantity) to the upper third of the panel and requires the use of small text size for some items (namely strength) to communicate all of the information in that area. DMETS believes that close proximity of the information and the small text size makes the information difficult to read, and recommends that the pharmacy label area not be designated on the principle display panel of the carton.

3.2 POUCH LABELING

DMETS noted that the text used to display the strength on the patch label is smaller than the text used to display the proprietary and established name and a different color. DMETS believes that this makes this critical information difficult to locate and read (see image below).



3.3 SPONSOR'S PHYSICIAN/PATIENT EDUCATION PLAN OVERVIEW

DMETS believes that the concepts presented in the Sponsor's proposed education plan may help to address the risks and safety concerns with the proposed Exelon Patch that were noted in OSE Review 2007-532 & 2006-704. However, on DMETS did have two areas of concern with the description of the educational pieces on Page 3.

First, the description of the Starter Kit refers to a "Patch Cutter". In other materials the device is referred to as a "Pouch Opener". DMETS believes that consistent use of the "Pouch Opener" term is desirable, otherwise patients or practitioners may be mistakenly led to believe that the Exelon Patches can be cut. DMETS has further concerns about the "Pouch Opener" device, which are discussed in detail below Section 4.4.

Secondly, DMETS noted that a "How to Apply Video" will be available for practitioners in October 2007 but not for patients and caregivers until "early 2008" on the Sponsor's website. New users of other transdermal products have had difficulty properly applying transdermal systems, particularly those users with no prior experience using transdermal systems. DMETS believes that if this video can be made available sooner (i.e. at the same time it becomes available to practitioners), this resource may help to reduce user errors when applying Exelon Patch.

Lastly, DMETS noted that the Sponsor is including a survey element in the "Early Experience Starter Kit" for physicians to track their patient's experience on Exelon Patch. DMETS does not have concern with this proposed survey from a safety standpoint, but does believe that the information that the Sponsor intends to collect from this survey could be of interest to the Agency. The Sponsor did not indicate in the plan if they intend to share this information with the Agency, but DMETS believes that the Sponsor should be encouraged to do so since the Exelon Patch, if approved, will be the first transdermal system used for Alzheimer's disease.

3.4 SPONSOR'S PATIENT COMMUNICATION PLAN OVERVIEW

DMETS reviewed the overview of the Sponsor's Patient Communication Plan, but did not review the individual pieces (i.e. video, kit components, etc), as these were not provided. However DMETS has identified some areas of concern, based on the description of the items or images submitted to the Agency. The main safety concerns were noted with the Starter Kit components which include 4 weeks of titration samples, "a "Patch cutter/Pouch opener/ExelonPATCH Opener", "How to use Exelon Patch Opener instructions" "Patch Holder", "Days of the week stickers," and various written materials (letter, brochure, prescribing information, enrollment card). DMETS main concerns regard the inclusion of a pouch opening device and the stickers. DMETS also questions if the titration samples will be the 4.6 mg/24 hour strength, and if so please specify.

DMETS is particularly concerned with the Sponsor's proposal to include a "Pouch Opener" device. DMETS has not seen the actual device, and is worried that the device could damage the Exelon Patch when opening the pouch. Furthermore the proposed instructions for use and pouch label tell patients to cut open the patch with scissors not a "Pouch Opener."

DMETS is also concerned that the "Days of the Week Stickers" could introduce errors. Patients or caregivers could mistakenly apply the wrong "Day of the Week" sticker and which could lead to confusion. The stickers could also be mistaken as the medication itself, particularly since they are the same circular shape of the Exelon Patch. Lastly, it seems that the Sponsor is proposing that the stickers be applied to either the pouch or the actual Exelon Patch. DMETS is concerned that applying the sticker to the patch may

obscure the identification of the Patch in an emergency situation, and could inadvertently mislead patients and caregivers to believe that the use of overlays over the Patch is a safe practice.

DMETS acknowledges that the stickers are intended to help patients and caregivers keep track of Exelon Patch applications, but DMETS does not believe that this purpose is well-served by the stickers. DMETS also noted that the Exelon Patch Holder has a similar function, and does not seem to introduce any additional risks.

3.5 NOVARTIS PROPOSAL FOR USE OF CURRENT STOCK OF EXELON PATCHES

DMETS is concerned that the distribution of the 4.6 mg/24 hour patches that were manufactured prior to the label modifications could create confusion in the marketplace if patients and caregivers become accustomed to the appearance and then subsequent patches are different.

However, DMETS believes that the Sponsor's proposal to restrict the majority of the completed Exelon Patch 4.6 mg/24 hour product to sample distribution is reasonable, and should help to minimize confusion since this will not be the customary distribution channel by which patients receive the product.

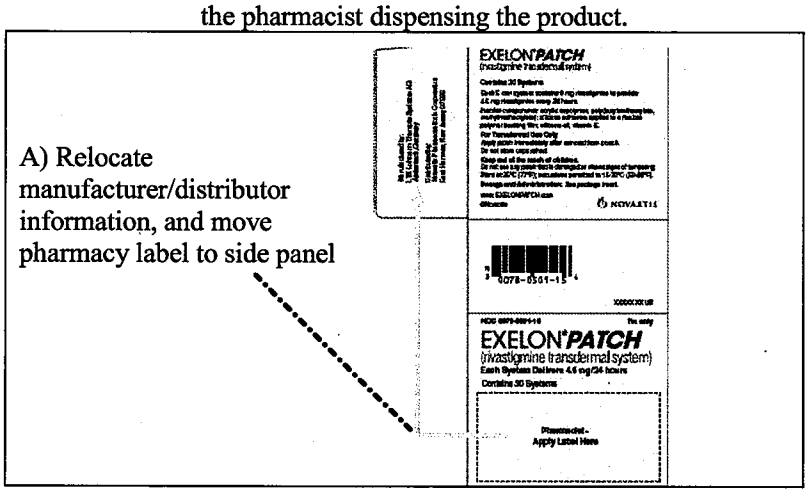
DMETS is concerned that the Sponsor did not specify how 30% of the Samples will be packaged, and would need further information on this before commenting on the overall risk of using the completed product for sample distribution.

4 CONCLUSIONS AND RECOMMENDATIONS

4.1 CARTON LABELING

1. DMETS recommends that the Sponsor consider relocating the manufacturer/distributor information (See image below, A) and relocating the pharmacy label area to the side.

   If the Sponsor does not find this side panel to be a suitable alternate location to designate as the pharmacy label area, DMETS recommends that the Sponsor forgo designating a space to affix the pharmacy label and leave this matter up to the pharmacist dispensing the product.



2. Increase the text size of the strength (i.e. "9.5 mg /24 hours"). DMETS recommends that text size should be equal to the established name so that the information can be easily located on the primary display panel. This modification may also require widening of the white band to accommodate this change.
3. The Sponsor may also wish to consider increasing the prominence of the strength (only the mg/24 hour portion) by bolding, the use of color or some other means to improve readability.
4. Relocate the container quantity (i.e. "Contains 30 systems") to the lower portion of the display panel.

4.2 POUCH LABELING

1. Increase the text size of the strength (i.e. "9.5 mg /24 hours"). DMETS recommends that text size should be equal to the established name so that the information can be easily located on the primary display panel. The Sponsor may also wish to consider increasing the prominence of the strength (only the mg/24 hour portion) by highlighting or some other means.

4.3 SPONSOR'S PHYSICIAN/PATIENT EDUCATION PLAN OVERVIEW

1. DMETS recommends that the "How to Apply Video" be available as early as possible as a resource for patients.
2. DMETS encourages the Sponsor to share the information acquired from the survey element of the "Early Experience Starter Kit" with the Agency.

4.4 SPONSOR'S PATIENT COMMUNICATION PLAN OVERVIEW

1. DMETS recommends that the Sponsor specify the strength of the titration samples to be included in the Starter Kit. DMETS has assumed that the strength will be the 4.6 mg/24 hour product.
2. DMETS recommends that the Sponsor's submit the proposed "Pouch Opener" device for review or omit this device from the Starter Kit. Additionally, if the device is included, please use consistent language when describing the device and avoid the term "Patch Cutter".
3. DMETS strongly recommends that the "Days of the Week Stickers" be excluded from any materials provided to patients, caregivers, or practitioners

4.5 NOVARTIS PROPOSAL FOR USE OF CURRENT STOCK OF EXELON PATCHES

1. DMETS does not object to the concept of distributing the completed patch product as samples but requests further information before an overall risk assessment of the proposal. In particular, it is not clear from the proposal what type of container 30% of the samples will be packaged.

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/s/

Kellie Taylor
6/27/2007 05:44:45 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/28/2007 07:50:09 AM
DRUG SAFETY OFFICE REVIEWER

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

CLINICAL INSPECTION SUMMARY

DATE: May 14, 2007

TO: Melina Griffis, Regulatory Project Manager
Ranjit Mani, M. D., Medical Officer
Division of Neurology Products, HFD-120

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-083

APPLICANT: Novartis Pharmaceuticals Corp.

DRUG: Exelon Patch (rivastigmine) once daily

THERAPEUTIC CLASSIFICATION: Priority Review (6 months)

INDICATIONS: Mild to moderate Alzheimer's disease and mild to moderate Parkinson's disease dementia.

CONSULTATION REQUEST DATE: October 18, 2006

DIVISION ACTION GOAL DATE: June 8, 2007

PDUFA DATE: July 8, 2007

I. BACKGROUND:

The review division requested inspection of protoc[redacted]3D2320: "A 24-week, multicenter, randomized, double-blind, placebo and active-controlled, parallel-group evaluation of the efficacy, safety and tolerability of the once-daily Exelon patch formulation in patients with probable Alzheimer's disease (MMSE 10-20)". The sponsor submitted results from the following two sites in support of NDA 22-083. The inspections targeted two clinical investigators who enrolled a relatively large number of subjects.

b(4)

The following two clinical investigators were selected for data audit in support of this application:

Site# 0134 (Andrzej Potemkowski, M.D. - Poland)
Site# 0152 (Nikolai Yakhno, M.D. – Russia)

II. RESULTS (by protocol/site):

Name of CI and site #, if known	Country	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Andrzej Potemkowski, M.D. Site #0134	Poland	Pamieci	[redacted] 713D 2320	2/12/07	pending	NAI*
Nikolai Yakhno, M.D Site# 0152	Russia	Moscow	[redacted] 713D 2320	2/19/07	pending	VAI*

b(4)

* based on e-mail summary information or telephone call from the field investigators.

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

Protocol CENA713D2320

1. Andrzej Potemkoski, M.D.

   Observations noted below are based on a telephone message from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

   At this site a total of 44 subjects were screened, 3 subjects were reported as screen failures, 44 subjects signed informed consent, and 41 subjects were randomized and completed the study. All 44 subjects were verified to have signed informed consent prior to entry into the study. The medical records for 20 subjects were reviewed in depth and compared to case report forms and data listings for primary efficacy end points and adverse events.

   The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and no significant problems were found that would impact the results. There were no known limitations to this inspection.

   The data appear acceptable in support of the pending application.

2. Nikolai Yakhno, M.D.

   Observations noted below are based on an e-mail summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

   At this site a total of 45 subjects were screened, 7 subjects were screen failures, and 38 subjects were randomized and completed the study. The medical records for 19 subjects were reviewed. Informed consent for all subjects was verified and minor regulatory violations were found. These include failure to re-consent one subject with the revised IRB approved informed consent, and five

subjects signed the consent form after the study was completed. There was no underreporting of adverse events. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Dr. Yakhno revealed problems with the informed consent procedures. However, in general these deviations do not adversely impact data acceptability. The data submitted are acceptable in support of the pending application

The inspection of Dr. Potemkowski revealed no significant problems that would adversely impact data acceptability. Therefore, the data from this site are acceptable in support of the pending application.

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Antoine El-Hage
5/23/2007 08:21:35 AM
PHARMACOLOGIST

Constance Lewin
5/23/2007 10:55:22 AM
MEDICAL OFFICER

Executive CAC Meeting Minutes

Date of Meeting: May 1, 2007

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Joseph Contrera, Ph.D., OPS, Member
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., DDDP, Alternate Member
Lois Freed, Ph.D., DNP, Supervisor
David Hawver, Ph.D., DNP, Presenting Reviewer

Author of Draft: David Hawver, Ph.D.

The following information reflects a brief summary of the Committee's discussion and its recommendations.

NDA #: 22-083
Drug Name: Exelon® Patch, Rivastigmine
Sponsor: Novartis Pharma AG

Background:
Oral rivastigmine is a cholinesterase inhibitor currently marketed for the treatment of dementia of Alzheimer's disease and Parkinson's disease. A 99-week dermal carcinogenicity study in mouse was submitted to support an NDA for a new dermal formulation of rivastigmine, Exelon® Patch.

Mouse Dermal Carcinogenicity Study:
CD-1 mice (50/sex/group) were treated with rivastigmine via dermal application in 100% ethanol at doses of 0, 0.25, 0.50, and 0.75 mg/kg/day once daily for 99 weeks; an untreated control group was also included. The high dose of 0.75 mg/kg/day was expected to be close to the maximum tolerated dose (MTD), since a single dermal dose of 1.6 mg/kg/day rivastigmine was lethal in a previous 13-week mouse study. The carcinogenicity study appeared to be adequately performed. No treatment-related neoplastic or non-neoplastic findings were observed. The Statistical Reviewer concurred that no treatment-related neoplastic findings were observed.

Executive CAC Recommendations and Conclusions:

- The Committee noted that the study was terminated early (at Week 99) based on survival in control groups reaching 25/50. Although this is not considered sufficient cause for early termination, the Committee concluded that the study was adequate.

- The Committee agreed that doses were appropriate and that the study was negative for carcinogenicity since there were no treatment-related tumor findings.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\
/division file, DNP
/LMFreed/Supervisor, DNP
/DHawver, DNP
/MGriffis/CSO, DNP
/ASeifried, OND IO

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/s/

David Jacobson-Kram
5/14/2007 10:41:57 AM

MEMORANDUM

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

DATE: April 26, 2007

TO: Russell Katz, M.D., Director
Division of Neurology Products

VIA: Melina Griffis, Regulatory Project Manager
Division of Neurology Products

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

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

SUBJECT: OSE/DSRCS Review of Patient Labeling for Exelon Patch (rivastigmine) transdermal system, NDA 22-083

Background and Summary

Novartis Pharmaceutical Corporation submitted an NDA on September 8, 2006, for Exelon Patch (rivastigmine) transdermal system, NDA 22-083, for the treatment of mild to moderate Alzheimer's disease and mild to moderate Parkinson's disease dementia.

Patient Labeling in the form of a Patient Package Insert (PPI) was submitted with the NDA and consulted to DSRCS for review.

Comments and Recommendations

1. See the attached documents (marked and clean copies) for our recommended revisions to the draft PPI. We have simplified language to enhance readability, ensured the information is consistent with the information in the prescribing information (PI), and removed unnecessary information. Our revisions lowered the reading level from a grade level of 10.8 (Flesh-Kincaid) to a grade level of 5.8. To enhance comprehension, patient information should be written at an 8th grade reading level or less. All of our recommended changes are consistent with current research to improve risk communication to a broad audience of varying educational backgrounds including those with lower literacy.

2. Refer to the FPI, Highlights of Prescribing Information, **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."** Revise the term **'Medication Guide' to 'FDA Approved Patient Labeling'.** A Medication Guide was not submitted, nor requested for the product, and the regulatory requirements set forth in 21 § 208 (Medication

Guide Regulations) are not met with the information presented in this NDA.

3. Refer to the FPI, section 17, **PATIENT COUNSELING INFORMATION**. This section is deficient in that it contains no counseling information for prescribers to provide to patients. This section should be written and directed to the prescriber, not to the patient. FDA Approved Patient Labeling should be referenced in, and either follows this section or accompanies the FPI [see 201.57(18)]. Revise the FPI, **PATIENT COUNSELING INFORMATION,** to contain appropriate information for prescribers to counsel patients.

4. We recommend, though not required, that the sponsor print the PPIs using at least a 10-point font. This medication will be used mainly in an older population and research has shown that most older people cannot easily read font printed smaller than 12-point

Comments to the review division in the attached documents are ***bolded, underlined and italicized***. Please call us if you have any questions.

8 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Jeanine Best
4/26/2007 08:48:24 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
4/27/2007 08:58:47 AM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		**REQUEST FOR CONSULTATION**		
TO *(Division/Office)*: HFD-420/Director, Division of Medication Errors and Technical Support			FROM: HFD-120/Division of Neurology Products	
DATE: 3/6/07	IND NO.:	NDA NO.: NDA 22-083	TYPE OF DOCUMENT: New Label- Revised Carton, Container & Packaging Labels for Review	DATE OF DOCUMENT:
NAME OF DRUG: Exelon Patch Transdermal System	PRIORITY CONSIDERATION: User fee due date is 7/8/07		CLASSIFICATION OF DRUG: Alzheimer's Disease	DESIRED COMPLETION DATE: May 1 ,2007
NAME OF FIRM: Novartis Pharmaceuticals				

COMMENTS/SPECIAL INSTRUCTIONS:

The sponsor has submitted a labeling amendment to provide revised carton and container labels and more detailed packaging information for this NDA. The EDR link to the submission is:

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SIGNATURE OF REQUESTER: Melina Griffis (301-796-1078)	METHOD OF DELIVERY (Check one): MAIL ☐ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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/s/

Melina Griffis
3/7/2007 09:21:35 AM