CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22-083/S016

Trade Name: Exelon Patch

Generic Name: rivastigmine transdermal system

Sponsor: Novartis Pharmaceuticals Corp.

Approval Date: August 31, 2012

Indications: For the treatment of mild to moderate dementia associated with Parkinson's disease (PDD).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22083/S-016

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Peter D. McArdle, DVM
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. McArdle:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 31, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exelon® Patch (rivastigmine transdermal system) 13.3 mg/24 hours.

We acknowledge receipt of your amendments dated:

February 14, 2012	March 22, 2012	April 4, 2012
April 5, 2012	April 12, 2012	July 6, 2012
July 13, 2012	August 17, 2012	August 23, 2012
August 28, 2012		

This "Prior Approval" supplemental new drug application provides for the following:

- a new dosage strength of the transdermal formulation (13.3 mg/24 hours nominal release rate, 27 mg total drug load, 15cm2 patch size) for use in the currently approved indications for the treatment of mild to moderate dementia of the Alzheimer's type (AD)
- and for the treatment of mild to moderate dementia associated with Parkinson's disease (PDD)

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any

labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 31, 2012 and April 5, 2012, submissions containing final printed carton and container labels. We remind you of your August 6, 2012 agreement with DMEPA that, at product launch, the configuration would consisting of cartons containing the FDA requested changes and pouches using a format and layout based upon the currently approved strengths, and the final requested packaging configuration (revised carton & revised foil) should be introduced to the market by January 2013.

Submit final printed carton and container labels that are identical to those described above as soon as they are available, but no more than 30 days after they are printed.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because the disease does not exist in children.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

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

If you have any questions, call Teresa Wheelous, Regulatory Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
08/31/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXELON PATCH safely and effectively. See full prescribing information for EXELON PATCH.

EXELON PATCH (rivastigmine transdermal system)
Initial U.S. Approval: 2000

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.1) ---------- 08/2012

----------INDICATIONS AND USAGE----------
Exelon Patch is an acetylcholinesterase inhibitor indicated for treatment of:

- Mild to moderate dementia of the Alzheimer's type (1.1)
- Mild to moderate dementia associated with Parkinson's disease (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Apply patch on intact skin for a 24-hour period; replace with a new patch every 24 hours (2.1)
- Initiate treatment with 4.6 mg/24 hours Exelon Patch (2.1)
- After a minimum of 4 weeks, if tolerated, increase dose to 9.5 mg/24 hours, which is the minimum effective dose (2.1)
- Following a minimum additional 4 weeks, may increase dosage to maximum dosage of 13.3 mg/24 hours (2.1)
- For treatment interruption longer than three days, retitrate dosage starting at 4.6 mg/24 hours (2.1)
- Consider dose adjustments in patients with (2.2):
  Moderate to severe renal impairment
  Mild to moderate hepatic impairment
  Low (<50 kg) body weight
-

----------DOSAGE FORMS AND STRENGTHS----------
Exelon Patch 4.6 mg/24 hours or 9.5 mg/24 hours or 13.3 mg/24 hours (3)

----------CONTRAINDICATIONS----------
Patients with known hypersensitivity to rivastigmine, other carbamate derivatives, or other components of the formulation (4, 6.2)

----------WARNINGS AND PRECAUTIONS----------

- *Overdose from medication errors* Hospitalization and, rarely, death have been reported due to application of multiple patches at same time. Ensure patients or caregivers receive instruction on proper dosing and administration. (5.1)
- *Gastrointestinal adverse reactions* May include significant nausea, vomiting, diarrhea, anorexia/decreased appetite, and weight loss, and may necessitate treatment interruption. Dehydration may result from prolonged vomiting or diarrhea and can be associated with serious outcomes. (5.2)

----------ADVERSE REACTIONS----------
Most commonly observed adverse reactions (>5% and higher than with placebo): Nausea, vomiting, and diarrhea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Cholinomimetic and anticholinergic drugs Avoid concomitant use unless clinically necessary (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: August 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Alzheimer's Disease

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

1.2 Parkinson's Disease Dementia

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The effective dosage of Exelon Patch is 9.5 mg/24 hours or 13.3 mg/ 24 hours administered once per day; replace with a new patch every 24 hours.

Initial Dose

Initiate treatment with one 4.6 mg/24 hours Exelon Patch applied to the skin once daily *[see Dosage and Administration (2.4)]*.

Dose Titration

Increase the dose only after a minimum of 4 weeks at the previous dose, and only if the previous dose has been well tolerated. Continue the recommended effective dose of 9.5 mg/24 hours for as long as therapeutic benefit persists. Patients can then be increased to the maximum effective dose of 13.3 mg/24 hours dose. Doses higher than 13.3 mg/24 hours confer no appreciable additional benefit, and are associated with an increase in the incidence of adverse reactions *[see Warnings and Precautions (5.2), Adverse Reactions (6.1)]*.

Interruption of Treatment

If dosing is interrupted for three days or fewer, restart treatment with the same or lower strength Exelon Patch. If dosing is interrupted for more than three days, restart treatment with the 4.6 mg/24 hours Exelon Patch and titrate as described above.

2.2 Dosing in Specific Populations

Dosing Modifications in Patients with Renal or Hepatic Impairment

Consider using the 4.6 mg/24 hours Exelon Patch as both the initial and **maximum** dose in patients with moderate to severe renal impairment and in patients with mild to moderate hepatic impairment. Pharmacokinetic studies of oral rivastigmine in these patient populations showed reduced clearance of the drug *[see Use in Specific Populations (8.6, 8.7), Clinical Pharmacology (12.3)]*.

Dosing Modifications in Patients with Low Body Weight

Because rivastigmine blood levels vary with weight *[see Use in Specific Populations (8.8), Clinical Pharmacology (12.3)]*, carefully titrate and monitor patients with low body weight (<50kg) for toxicities (e.g., excessive nausea, vomiting) and consider reducing the maintenance dose to the 4.6 mg/24 hours Exelon Patch if such toxicities develop.

2.3 Switching to Exelon Patch from Exelon Capsules or Exelon Oral Solution

Patients treated with Exelon capsules or oral solution may be switched to Exelon Patch as follows:

- A patient who is on a total daily dose of <6 mg of oral rivastigmine can be switched to the 4.6 mg/24 hours Exelon Patch.
- A patient who is on a total daily dose of 6-12 mg of oral rivastigmine can be switched to the 9.5 mg/24 hours Exelon Patch.

Instruct patients or caregivers to apply the first patch on the day following the last oral dose.

2.4 Important Administration Instructions

Exelon Patch is for transdermal use on intact skin.

(a) Do not use the patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

(b) Apply the Exelon Patch once a day

- Press down firmly until the edges stick well when applying to clean, dry, hairless, intact healthy skin in a place that will not be rubbed against by tight clothing.
- Use the upper or lower back as the site of application because the patch is less likely to be removed by the patient. If sites on the back are not accessible, apply the patch to the upper arm or chest.
- Do not apply to a skin area where cream, lotion, or powder has recently been applied.

(c) Do not apply to skin that is red, irritated, or cut.

(d) Replace the Exelon Patch with a new patch every 24 hours. If taking 4.5 mg/24 hours, instruct patients to only wear one patch at a time (remove the previous day's patch before applying a new patch) *[see Warnings and Precautions (5.1) and Overdosage (10)]*. If a dose is missed, apply a new patch immediately.

(e) Change the site of patch application daily to minimize potential irritation, although a new patch can be applied to the same general anatomic site (e.g., another spot on the upper back) on consecutive days. Do not apply a new patch to the same location for at least 14 days.

(f) May wear the patch during bathing and in hot weather. But avoid long exposure to external heat sources (excessive sunlight, saunas, solariums).

(g) Place used patches in the previously saved pouch and discard in the trash, away from pets or children.

3 DOSAGE FORMS AND STRENGTHS

Exelon Patch is available in three strengths. Each patch has a beige backing layer labeled as either:

- EXELON® PATCH 4.6 mg/24 hours, AMCX
- EXELON® PATCH 9.5 mg/24 hours, BHDI
- EXELON® PATCH 13.3 mg/24 hours, CNFU

4 CONTRAINDICATIONS

Exelon Patch (rivastigmine transdermal system) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives, or other components of the formulation [see *Description (11)*]. Isolated cases of generalized skin reactions have been described in post-marketing experience [see *Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Medication Errors Resulting in Overdose

Medication errors with Exelon Patch have resulted in serious adverse reactions; some cases have required hospitalization, and rarely, led to death. The majority of medication errors have involved not removing the old patch when putting on a new one and the use of multiple patches at one time. Instruct patients and their caregivers on important administration instructions for Exelon Patch. *[see Dosage and Administration (2.4)]*.

5.2 Gastrointestinal Adverse Reactions

Exelon Patch can cause gastrointestinal adverse reactions, including significant nausea, vomiting, diarrhea, anorexia/decreased appetite, and weight loss. Dehydration may result from prolonged vomiting or diarrhea and can be associated with serious outcomes. The incidence and severity of these reactions are dose-related *[see Adverse Reactions (6.1)]*. For this reason, initiate treatment with Exelon Patch at a dose of 4.6 mg/24 hours and titrate to a dose of 9.5 mg/24 hours and then to a dose of 13.3 mg/24 hours, if appropriate *[see Dosage and Administration (2.1)]*.

If treatment is interrupted for more than three days because of intolerance, reinitiate Exelon Patch with the 4.6 mg/24 hours dose to reduce the possibility of severe vomiting and its potentially serious sequelae. A postmarketing report described a case of severe vomiting with esophageal rupture following inappropriate

reinitiation of treatment of an oral formulation of rivastigmine without retitration after 8 weeks of treatment interruption.

Inform caregivers to monitor for gastrointestinal adverse reactions and to inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than three days because of intolerance, the next dose should not be administered without contacting the physician regarding proper retitration.

5.3 Other Adverse Reactions from Increased Cholinergic Activity

Neurologic Effects

Extrapyramidal Symptoms: Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening of parkinsonian symptoms, particularly tremor, has been observed in patients with dementia associated with Parkinson's disease who were treated with Exelon capsules.

Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's disease.

Peptic Ulcers/Gastrointestinal Bleeding

Cholinesterase inhibitors, including rivastigmine, may increase gastric acid secretion due to increased cholinergic activity. Monitor patients using Exelon Patch for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical studies of rivastigmine have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Use with Anesthesia

Rivastigmine, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiac Conduction Effects

Because rivastigmine increases cholinergic activity, use of the Exelon Patch may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important in patients with sick sinus syndrome or other supraventricular cardiac conduction conditions. In clinical trials, rivastigmine was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities.

Genitourinary Effects

Although not observed in clinical trials of rivastigmine, drugs that increase cholinergic activity may cause urinary obstruction.

Pulmonary Effects

Like other drugs that increase cholinergic activity, Exelon Patch should be used with care in patients with a history of asthma or obstructive pulmonary disease.

5.4 Impairment in Driving or Use of Machinery

Dementia may cause gradual impairment of driving performance or compromise the ability to use machinery. The administration of rivastigmine may also result in adverse reactions that are detrimental to these functions. During treatment with the Exelon Patch, routinely evaluate the patient's ability to continue driving or operating machinery.

6 ADVERSE REACTIONS

Significant gastrointestinal adverse reactions including nausea, vomiting, anorexia, and weight loss are described below and elsewhere in the labeling *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Exelon Patch has been administered to 1634 patients with Alzheimer's disease during clinical trials worldwide. Of these, 1388 patients have been treated for at least 12 weeks, 1182 patients have been treated for at least 24 weeks, and 582 patients have been treated for at least 48 weeks.

24-Week International Placebo-Controlled Trial (Study 1)

Most Commonly Observed Adverse Reactions

The most commonly observed adverse reactions in patients administered Exelon Patch in Study 1 *[see Clinical Studies (14.1)]*, defined as those occurring at a frequency of at least 5% in the 9.5 mg/24 hours Exelon Patch arm and at a frequency at higher than in the placebo group, were nausea, vomiting, and diarrhea. These reactions were dose-related, with each being more common in patients using the 17.4 mg/24 hours Exelon Patch than in those using the 9.5 mg/24 hours Exelon Patch.

Discontinuation Rates

In Study 1, which randomized a total of 1195 patients, the proportions of patients in the Exelon Patch 9.5 mg/24 hours, Exelon capsules 6 mg twice daily, and placebo groups who discontinued treatment due to adverse events were 9.6%, 8.1%, and 5.0%, respectively.

The most common adverse reactions in the Exelon Patch-treated groups that led to treatment discontinuation in this study were nausea and vomiting. The proportions of patients who discontinued treatment due to nausea were 0.7%, 1.7%, and 1.3% in the Exelon Patch 9.5 mg/24 hours, Exelon capsules 6 mg twice daily, and placebo groups, respectively. The proportions of patients who discontinued treatment due to vomiting were 0%, 2.0%, and 0.3% in the Exelon Patch 9.5 mg/24 hours, Exelon capsules 6 mg twice daily, and placebo groups, respectively.

Adverse Reactions Observed at an Incidence of ≥2%

Table 1 lists adverse reactions seen at an incidence of ≥2% in either Exelon Patch-treated group in Study 1 and for which the rate of occurrence was greater for patients treated with that dose of Exelon Patch than for those treated with placebo. The unapproved 17.4 mg/24 hours Exelon Patch arm is included to demonstrate the increased rates of gastrointestinal adverse reactions over those seen with the 9.5 mg/24 hours Exelon Patch.

Table 1: Proportion of Adverse Reactions Observed with a Frequency of ≥2% and Occurring at a Rate Greater Than Placebo in Study 1

				Placebo
Total Patients Studied	291	303	294	302
Total Percentage of Patients with ARs (%)	51	66	63	46
Nausea	7	21	23	5
Vomiting*	6	19	17	3
Diarrhea	6	10	5	3
Depression	4	4	4	1
Headache	3	4	6	2
Anxiety	3	3	2	1
Anorexia/Decreased Appetite	3	9	9	2
Weight Decreased **	3	8	5	1
Dizziness	2	7	7	2
Abdominal Pain	2	4	1	1
Urinary Tract Infection	2	2	1	1
Asthenia	2	3	6	1

Fatigue	2	2	1	1
Insomnia	1	4	2	2
Abdominal Pain Upper	1	3	2	2
Vertigo	0	2	1	1

*Vomiting was severe in 0% of patients who received Exelon Patch 9.5 mg/24 hours, 1% of patients who received Exelon Patch 17.4 mg/24 hours, 1% of patients who received the Exelon capsule at doses up to 6 mg BID, and 0% of those who received placebo.

**Weight Decreased as presented in Table 1 is based upon clinical observations and/or adverse events reported by patients or caregivers. Body weight was also monitored at pre-specified time points throughout the course of the clinical study. The proportion of patients who had weight loss equal to or greater than 7% of their baseline weight was 8% of those treated with Exelon Patch 9.5 mg/24 hours, 12% of those treated with Exelon Patch 17.4 mg/24 hours, 11% of patients who received the Exelon capsule at doses up to 6 mg BID and 6% of those who received placebo. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.

48-Week International Active Comparator-Controlled Trial (Study 2)

Most Commonly Observed Adverse Reactions

In Study 2 *[see Clinical Studies (14.2)]* of the commonly observed adverse reactions (≥ 3% in any treatment group) the most frequent event in the Exelon Patch 13.3 mg/24 hours group was nausea, followed by vomiting, fall, weight decreased, application site erythema, decreased appetite, diarrhea and urinary tract infection (Table 2). The percentage of patients with these events was higher in the Exelon Patch 13.3 mg/24 hours group than in the Exelon Patch 9.5 mg/24 hours group. Patients with nausea, vomiting, diarrhea and decreased appetite experienced these reactions more often during the first 4 weeks of the double-blind treatment phase. These reactions decreased over time in each treatment group. Weight decreased was reported to have increased over time in each treatment group.

Discontinuation Rates

Table 2 displays the most common adverse reactions leading to discontinuation during the 48-week double-blind treatment phase in Study 2.

Table 2: Proportion of Most Common Adverse Reactions (>1% at any dose) Leading to Discontinuation During 48-week Double Blind Treatment Phase in Study 2

	Exelon Patch 13.3 mg/24 hours	Exelon Patch 9.5 mg/24 hours	Total
Total Patients Studied	280	283	563
Total Percentage of Patients with ARs Leading to Discontinuation (%)	9.6	12.7	11.2
Vomiting	1.4	0.4	0.9
Application site pruritus	1.1	1.1	1.1
Aggression	0.4	1.1	0.7

Most Commonly Observed Adverse Reactions≥3%

Other adverse reactions of interest which occurred less frequently, but which were observed in a markedly higher percentage of patients in the Exelon Patch 13.3 mg/24 hours group than in the Exelon Patch 9.5 mg/24 hours group in Study 2, included dizziness and upper abdominal pain. The percentage of patients with these reactions decreased over time in each treatment group (Table 3). The majority of patients reported adverse events of mild to moderate severity. The adverse event severity profile was generally similar for both the Exelon Patch 13.3 mg/24 hours and 9.5 mg/24 hours groups.

Table 3: Proportion of Adverse Reactions Over Time in the 48-week Double Blind (DB) treatment phase (at least 3% in any Treatment Group) in Study 2

	Cumulative Week 0-48 (DB Phase)		Week 0- 24 (DB Phase)		Week > 24 to 48 (DB Phase)	
Preferred Term	Exelon Patch 13.3 mg/24 hours	Exelon Patch 9.5 mg/24 hours	Exelon Patch 13.3 mg/24 hours	Exelon Patch 9.5 mg/24 hours	Exelon Patch 13.3 mg/24 hours	Exelon Patch 9.5 mg/24 hours
Total Patients Studied	280	283	280	283	241	246
Total Percentage of Patients with ARs (%)	75	68	65	55	42	40
Nausea	12	5	10	4	4	2
Vomiting	10	5	9	3	3	2
Fall	8	6	4	4	4	3
Weight decreased*	7	3	3	1	5	2
Application site erythema	6	6	6	5	1	2
Decreased appetite	6	3	5	2	2	<1
Diarrhea	6	5	5	4	2	<1
Urinary tract infection	5	4	3	3	3	2
Agitation	5	5	4	3	1	2
Depression	5	5	3	3	3	2
Dizziness	4	1	3	<1	2	<1
Application site pruritus	4	4	4	3	<1	1
Headache	4	4	4	4	<1	<1
Insomnia	4	3	2	1	3	2
Abdominal pain upper	4	1	3	1	1	<1
Anxiety	4	3	2	2	2	1
Hypertension	3	3	3	2	1	1
Urinary incontinence	3	2	2	1	1	<1
Psychomotor hyperactivity	3	3	2	3	2	1
Aggression	2	3	1	3	1	1

*Decreased Weight as presented in Table 3 is based upon clinical observations and/or adverse events reported by patients or caregivers. Body weight was monitored as a vital sign at pre-specified time points throughout the course of the clinical study. The proportion of patients who had weight loss equal to or greater than 7% of their baseline weight was 15.2% of those treated with Exelon Patch 9.5 mg/24 hours and 18.6% of those treated with Exelon Patch 13.3 mg/24 hours during the 48 week double-blind treatment period

Application Site Reactions in the 24-Week and 48-Week Studies (Studies 1 and 2)

A direct comparison of the rates of application site reactions reported in the placebo-controlled and active comparator controlled clinical trials cannot be made due to differences in the method of data collection employed in each of the trials.

In Study 1, cases of skin irritation were captured separately on an investigator-rated skin irritation scale and not as adverse events unless they fulfilled the criteria for a serious adverse event. Skin irritation, when observed, was mostly slight or mild in severity and was rated as severe in ≤2.2% of Exelon Patch patients, versus ≤1.0% of placebo patch patients. Among the skin reactions reported were the following: application site reactions, application site dermatitis and application site irritation.

In Study 2, cases of application site reactions were captured as patient or caregiver reported adverse events. The most commonly reported skin irritation events for both treatment groups were application site erythema and application site pruritus. These events occurred more frequently during the first 24 weeks of the double-blind period and decreased over time in each treatment group after 24 weeks (Table 3). The most common reason for discontinuation due to application site reactions was application site pruritus which occurred in 1.1% of the patients in each treatment group (Table 2). Application site reactions were mostly mild or moderate in severity and were rated as severe in less than 2% of patients.

Other Adverse Events Observed During Clinical Trials

The frequencies represent the proportion of 1634 patients from 2 controlled and 4 open-label trials in North America, Europe, Latin America, Asia and Japan who experienced that event while receiving Exelon Patch. All patch doses are pooled.

All adverse events occurring in approximately 0.1% are included, except for those already listed elsewhere in labeling, too general to be informative, or relatively minor events.

Events are classified by system organ class and listed using the following definitions: *Frequent* – those occurring in at least 1/100 patients; *Infrequent* – those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Exelon Patch treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Cardiac Disorders: *Infrequent*: Bradycardia, atrial fibrillation, atrioventricular block, arrhythmia, supraventricular extrasystole.

Ear and Labyrinth Disorders: *Infrequent*: Tinnitus.

Eye Disorders: *Infrequent*: Vision blurred.

Gastrointestinal System: *Frequent*: Constipation, gastritis. *Infrequent*: Gastroesophageal reflux disease, hematochezia, hematemesis, pancreatitis, salivary hypersecretion.

General Disorders and Administration Site Conditions: *Infrequent*: Chest pain.

Injury, Poisoning and Procedural Complications: *Infrequent*: Hip fracture.

Investigations: *Infrequent*: Blood creatine phosphokinase increased, lipase increased, blood amylase increased, electrocardiogram QT prolonged.

Metabolic and Nutritional Disorders: *Frequent*: Dehydration. *Infrequent*: Hypokalemia, hyponatremia.

Nervous System Disorders: *Infrequent*: Migraine.

Psychiatric Disorders: *Infrequent:* Delirium

Respiratory, Thoracic, and Mediastinal Disorders: *Infrequent*: Dyspnea, bronchospasm.

Skin and Subcutaneous Tissue Disorders: *Frequent*: Pruritus. *Infrequent*: Erythema, eczema, dermatitis, rash erythematous, skin ulcer.

Vascular Disorders: *Infrequent*: Hypotension, cerebrovascular accident.

Other Adverse Reactions Observed with Exelon Capsules or Oral Solution

The following additional adverse reactions have been observed with Exelon capsules/oral solution:

Confusion, abnormal liver function tests, duodenal ulcers, angina pectoris, myocardial infarction, tremor

6.2 Postmarketing Experience

The following additional adverse reactions have been identified based on postmarketing spontaneous reports and are not listed above. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypertension, application site hypersensitivity, urticaria, blister, allergic dermatitis, seizure, worsening of Parkinson's disease in patients with Parkinson's disease who were treated with Exelon Patch, tachycardia.

7 DRUG INTERACTIONS

7.1 Cholinomimetic and Anticholinergic Drugs

Rivastigmine may increase the cholinergic effects of other cholinomimetic drugs. Rivastigmine may also interfere with the activity of anticholinergic medications. Avoid concomitant use of rivastigmine with drugs having these pharmacologic effects unless deemed clinically necessary.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. No dermal reproduction studies in animals have been conducted. Oral reproduction studies conducted in pregnant rats and rabbits revealed no evidence of teratogenicity. Studies in rats showed slightly decreased fetal/pup weight, usually at doses causing some maternal toxicity. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Rivastigmine and its metabolites are excreted in rat milk following oral administration of rivastigmine; levels of rivastigmine plus metabolites in rat milk are approximately two times that in maternal plasma. It is not known whether rivastigmine is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Exelon Patch, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Use of Exelon Patch in children and adolescents (below 18 years of age) is not recommended.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of Exelon Patch, 88% were 65 and over, while 53% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

In patients with moderate to severe renal impairment (glomerular filtration rate [GFR] <50 mL/min), clearance of oral rivastigmine was reduced *[see Clinical Pharmacology (12.3)]*. In these patients, consider using the lowest dose Exelon Patch (4.6 mg/24 hours) for both initial and maintenance therapy.

8.7 Hepatic Impairment

In patients with mild or moderate hepatic impairment (Child-Pugh score 5-9), clearance of oral rivastigmine was reduced *[see Clinical Pharmacology (12.3)]*. In these patients, consider using the lowest dose Exelon Patch (4.6 mg/24 hours) for both initial and maintenance therapy. No data are available on the use of rivastigmine in patients with severe hepatic impairment.

8.8 Low or High Body Weight

Because rivastigmine blood levels vary with weight *[see Clinical Pharmacology (12.3)]*, careful titration and monitoring should be performed in patients with low or high body weights. In patients with low body weight

(<50 kg), monitor closely for toxicities (e.g., excessive nausea, vomiting), and consider reducing the maintenance dose to the 4.6 mg/24 hour Exelon Patch if such toxicities develop. In patients with body weight >100 kg, consider the use of doses higher than 9.5 mg/24 hours.

10 OVERDOSAGE

Overdose with Exelon Patch has been reported in the postmarketing setting *[see Warnings and Precautions (5.1)]*. Overdoses have occurred from application of more than one patch at one time and not removing the previous day's patch before applying a new patch. The symptoms reported in these overdose cases are similar to those seen in cases of overdose associated with rivastigmine oral formulations.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. As rivastigmine has a plasma half-life of about 3.4 hours after patch administration and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose the patch should be immediately removed and no further patch should be applied for the next 24 hours.

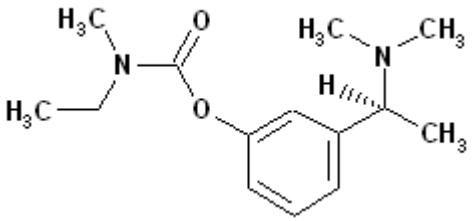
As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when coadministered with quaternary anticholinergics such as glycopyrrolate. Due to the short plasma elimination half-life of rivastigmine after patch administration, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.

In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered.

11 DESCRIPTION

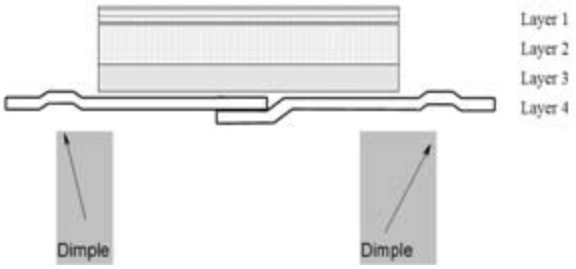
Exelon Patch (rivastigmine transdermal system) contains rivastigmine, a reversible cholinesterase inhibitor known chemically as (S)- 3-[1-(dimethylamino) ethyl]phenyl ethylmethylcarbamate. It has an empirical formula of $C_{14}H_{22}N_2O_2$ as the base and a molecular weight of 250.34 (as the base). Rivastigmine is a viscous, clear, and colorless to yellow to very slightly brown liquid that is sparingly soluble in water and very soluble in ethanol, acetonitrile, n-octanol and ethyl acetate.

The distribution coefficient at 37°C in n-octanol/phosphate buffer solution pH 7 is 4.27.



Exelon Patch is for transdermal administration. The patch is a four-layer laminate containing the backing layer, drug matrix, adhesive matrix and overlapping release liner (see Figure 1). The release liner is removed and discarded prior to use.

Figure 1: Cross Section of the Exelon Patch



Layer 1: Backing Film

Layer 2: Drug Product (Acrylic) Matrix

Layer 3: Adhesive (Silicone) Matrix

Layer 4: Release Liner (removed at time of use)

Excipients within the formulation include acrylic copolymer, poly(butylmethacrylate, methylmethacrylate), silicone adhesive applied to a flexible polymer backing film, silicone oil, and vitamin E.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Although the precise mechanism of action of rivastigmine is unknown, it is thought to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this mechanism is correct, the effect of rivastigmine may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process.

12.2 Pharmacodynamics

After a 6-mg oral dose of rivastigmine in humans, anticholinesterase activity is present in cerebrospinal fluid for about 10 hours, with a maximum inhibition of about 60% 5 hours after dosing.

In vitro and *in vivo* studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist.

12.3 Pharmacokinetics

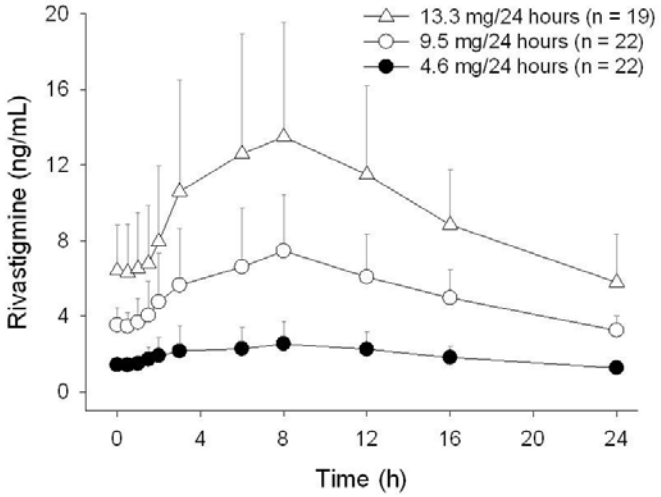
Absorption

After the initial application of Exelon Patch, there is a lag time of 0.5-1 hour in the absorption of rivastigmine. Concentrations then rise slowly typically reaching a maximum after 8 hours, although maximum values (C_{max}) can also occur later (at 10-16 hours). After the peak, plasma concentrations slowly decrease over the remainder of the 24-hour period of application. At steady state, trough levels are approximately 60-80% of peak levels.

Exelon Patch 9.5 mg/24 hours gave exposure approximately the same as that provided by an oral dose of 6 mg twice daily (i.e., 12 mg/day). Inter-subject variability in exposure was lower (43-49%) for the Exelon Patch formulation as compared with the oral formulations (73-103%). Fluctuation (between C_{max} and C_{min}) is less for Exelon Patch than for the oral formulation of rivastigmine.

Figure 2 displays rivastigmine plasma concentrations over 24 hours for the three available patch strengths.

Figure 2: Rivastigmine Plasma Concentrations Following Dermal 24-Hour Patch Application



Over a 24-hour dermal application, approximately 50% of the drug content of the patch is released from the system.

Exposure (AUC_∞) to rivastigmine (and metabolite NAP266-90) was highest when the patch was applied to the upper back, chest, or upper arm. Two other sites (abdomen and thigh) could be used if none of the three other sites is available, but the practitioner should be aware that the rivastigmine plasma exposure associated with these sites was approximately 20-30% lower.

There was no relevant accumulation of rivastigmine or the metabolite NAP226-90 in plasma in patients with Alzheimer's disease with daily dosing.

Distribution

Rivastigmine is weakly bound to plasma proteins (approximately 40%) over the therapeutic range. It readily crosses the blood-brain barrier, reaching CSF peak concentrations in 1.4-2.6 hours. It has an apparent volume of distribution in the range of 1.8-2.7 L/kg.

Metabolism

Rivastigmine is extensively metabolized primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite NAP226-90. *In vitro*, this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on evidence from *in vitro* and animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism.

The metabolite-to-parent AUC_∞ ratio was about 0.7 after Exelon Patch application versus 3.5 after oral administration, indicating that much less metabolism occurred after dermal treatment. Less NAP226-90 is formed following patch application, presumably because of the lack of presystemic (hepatic first pass) metabolism. Based on *in vitro* studies, no unique metabolic routes were detected in human skin.

Elimination

Renal excretion of the metabolites is the major route of elimination. Unchanged rivastigmine is found in trace amounts in the urine. Following administration of ^{14}C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the feces. The apparent elimination half-life in plasma is approximately 3 hours after patch removal. Renal clearance was approximately 2.1-2.8 L/hr.

Renal Impairment

No study was conducted with Exelon Patch in subjects with renal impairment. Following a single 3-mg dose, mean oral clearance of rivastigmine is 64% lower in moderately impaired renal patients (n=8, GFR=10-50 mL/min) than in healthy subjects (n=10, GFR≥60 mL/min); Cl/F=1.7 L/min and 4.8 L/min, respectively. In patients with severe renal impairment (n=8, GFR<10 mL/min), mean oral clearance of rivastigmine is 43% higher than in healthy subjects (n=10, GFR≥60 mL/min); Cl/F=6.9 L/min and 4.8 L/min, respectively. For unexplained reasons, the severely impaired renal patients had a higher clearance of rivastigmine than moderately impaired

patients. Despite this finding, consider a reduced dose in patients with moderate to severe renal impairment *[see Dosage and Administration (2.3)]*.

Hepatic Impairment

No pharmacokinetic study was conducted with Exelon Patch in subjects with hepatic impairment. After multiple 6-mg twice daily oral dosing, the mean clearance of rivastigmine was 65% lower in mild (n=7, Child-Pugh score 5-6) and moderate (n=3, Child-Pugh score 7-9) hepatically impaired patients (biopsy proven, liver cirrhosis) than in healthy subjects (n=10).

Body Weight

A relationship between drug exposure at steady state (rivastigmine and metabolite NAP226-90) and body weight was observed in Alzheimer's dementia patients. Rivastigmine exposure is higher in subjects with low body weight. Compared to a patient with a body weight of 65 kg, the rivastigmine steady-state concentrations in a patient with a body weight of 35 kg would be approximately doubled, while for a patient with a body weight of 100 kg the concentrations would be approximately halved *[see Dosage and Administration (2.3)]*.

Age

Age had no impact on the exposure to rivastigmine in Alzheimer's disease patients treated with Exelon Patch.

Gender or Race

No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of Exelon Patch. A population pharmacokinetic analysis of oral rivastigmine indicated that neither gender (n=277 males and 348 females) nor race (n=575 White, 34 Black, 4 Asian, and 12 Other) affected clearance of the drug. Similar results were seen with analyses of pharmacokinetic data obtained after the administration of Exelon Patch.

Smoking

Population pharmacokinetic analysis showed that nicotine use increased the oral clearance of rivastigmine by 23% (n=75 smokers and 549 nonsmokers).

Drug Interaction Studies

No specific interaction studies have been conducted with Exelon Patch. Information presented below is from studies with oral rivastigmine.

Effect of Rivastigmine on the Metabolism of Other Drugs

Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6.

No pharmacokinetic interaction was observed between rivastigmine taken orally and digoxin, warfarin, diazepam or fluoxetine in studies in healthy volunteers. The increase in prothrombin time induced by warfarin is not affected by administration of rivastigmine.

Effect of Other Drugs on the Metabolism of Rivastigmine

Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine.

Population pharmacokinetic analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine taken orally were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), ß-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35) and antihistamines (n=15).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In oral carcinogenicity studies conducted at doses up to 1.1 mg base/kg/day in rats and 1.6 mg base/kg/day in mice, rivastigmine was not carcinogenic.

In a dermal carcinogenicity study conducted at doses up to 0.75 mg base/kg/day in mice, rivastigmine was not carcinogenic. The mean rivastigmine plasma exposure (AUC) at this dose was less than that in humans at the maximum recommended human dose (13.3 mg/24 hours).

Mutagenesis

Rivastigmine was clastogenic in *in vitro* chromosomal aberration assays in mammalian cells in the presence, but not the absence, of metabolic activation. Rivastigmine was negative in an *in vitro* bacterial reverse mutation (Ames) assay, an *in vitro* HGPRT assay, and in an *in vivo* mouse micronucleus test.

Impairment of Fertility

No fertility or reproduction studies of dermal rivastigmine have been conducted in animals. Rivastigmine had no effect on fertility or reproductive performance in rats at oral doses up to 1.1 mg base/kg/day.

14 CLINICAL STUDIES

The effectiveness of the Exelon Patch in dementia of the Alzheimer's type and dementia associated with Parkinson's disease was based on the results of two controlled trials of Exelon Patch in patients with Alzheimer's disease (Studies 1 and 2) (see below); three controlled trials of oral rivastigmine in patients with dementia of the Alzheimer's type; and one controlled trial of oral rivastigmine in patients with dementia associated with Parkinson's disease. See the prescribing information for oral rivastigmine for details of the four studies of oral rivastigmine.

International 24-Week Study of Exelon Patch in Dementia of the Alzheimer's Type (Study 1)

This study was a randomized double-blind, double dummy clinical investigation in patients with Alzheimer's disease [diagnosed by NINCDS-ADRDA and DSM-IV criteria, Mini-Mental Status Examination (MMSE) score ≥10 and ≤20] (Study 1). The mean age of patients participating in this trial was 74 years with a range of 50-90 years. Approximately 67% of patients were women, and 33% were men. The racial distribution was White 75%, Black 1%, Asian 9%, and other races 15%.

The effectiveness of the Exelon Patch was evaluated in Study 1 using a dual outcome assessment strategy, evaluating for changes in both cognitive performance and overall clinical effect.

The ability of the Exelon Patch to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's disease patients. The ADAS-Cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language, and praxis. The ADAS-Cog scoring range is from 0-70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The ability of the Exelon Patch to produce an overall clinical effect was assessed using the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). The ADCS-CGIC is a more standardized form of the Clinician's Interview-Based Impression Of Change-Plus (CIBIC-Plus) and is also scored as a seven-point categorical rating; scores range from 1, indicating "markedly improved," to 4, indicating "no change," to 7, indicating "marked worsening."

In Study 1, 1195 patients were randomized to one of the following four treatments: Exelon Patch 9.5 mg/24 hours, Exelon Patch 17.4 mg/24 hours, Exelon capsules in a dose of 6 mg twice daily, or placebo. This 24-week study was divided into a 16-week titration phase followed by an 8-week maintenance phase. In the active treatment arms of this study, doses below the target dose were permitted during the maintenance phase in the event of poor tolerability.

Figure 3 illustrates the time course for the change from baseline in ADAS-Cog scores for all 4 treatment groups over the 24-week study. At 24 weeks, the mean differences in the ADAS-Cog change scores for the Exelon-treated patients compared to the patients on placebo, were 1.8, 2.9, and 1.8 units for the Exelon Patch 9.5 mg/24 hours, Exelon Patch 17.4 mg/24 hours, and Exelon capsule 6 mg twice daily groups, respectively. The

difference between each of these groups and placebo was statistically significant. Although a slight improvement was observed with the 17.4 mg/24 hours patch compared to the 9.5 mg/24 hours patch on this outcome measure, no meaningful difference between the two was seen on the global evaluation (see Figure 4).

Figure 3: Time Course of the Change from Baseline in ADAS-Cog Score for Patients Observed at Each Time Point in Study 1

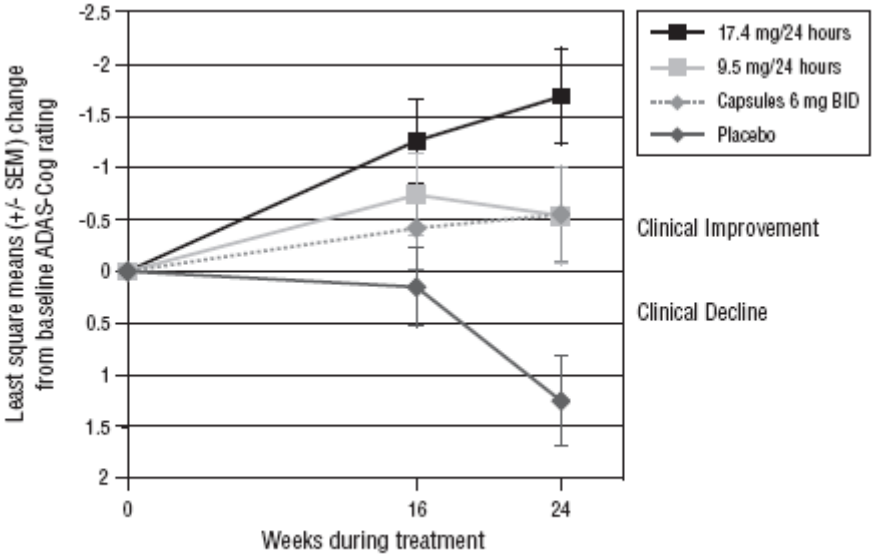
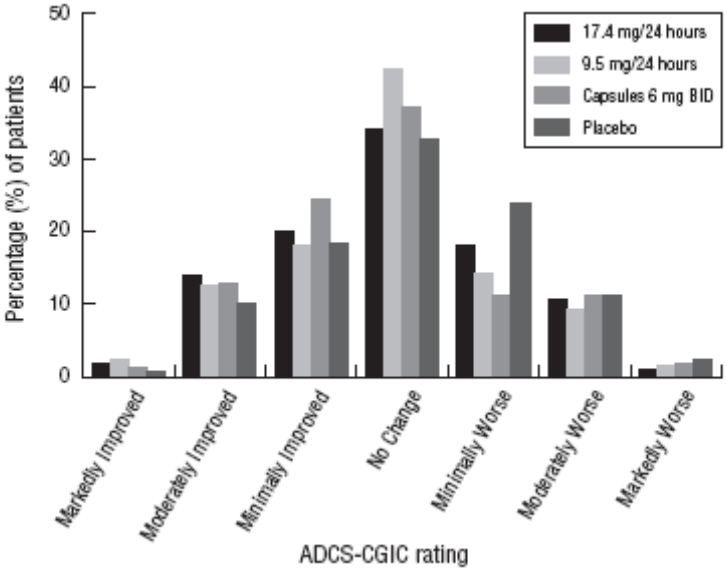


Figure 4 presents the distribution of patients' scores on the ADCS-CGIC for all 4 treatment groups. At 24 weeks, the mean difference in the ADCS-CGIC scores for the comparison of patients in each of the Exelon-treated groups with the patients on placebo was 0.2 units. The difference between each of these groups and placebo was statistically significant.

Figure 4: Distribution of ADCS-CGIC Scores for Patients Completing Study 1



International 48-Week Study of Exelon Patch in Dementia of the Alzheimer's Type (Study 2)

This study was a randomized double-blind clinical investigation in patients with Alzheimer's disease [diagnosed by NINCDS-ADRDA and DSM-IV criteria, Mini-Mental State Examination (MMSE) score ≥10 and ≤24] (Study 2). The mean age of patients participating in this trial was 76 years with a range of 50-85 years. Approximately 65% of patients were women and 35% were men. The racial distribution was approximately Caucasian 97%, Black 2%, Oriental 0.5% and Other Races 1%. Approximately 27% of the patients were taking memantine throughout the entire duration of the study.

Alzheimer's disease patients who received 24-48 weeks open label treatment with Exelon Patch 9.5mg/24 hours and who demonstrated functional and cognitive decline were randomized into treatment with either Exelon Patch 9.5 mg/24 hours or Exelon Patch 13.3 mg/24 hours in a 48-week double blind treatment phase. Functional decline was assessed by the investigator and cognitive decline was defined as a decrease in the MMSE score of ≥2 points from the previous visit or a decrease of ≥3 points from baseline.

Study 2 was designed to compare the efficacy of Exelon Patch 13.3 mg/ 24 hours versus that of Exelon Patch 9.5 mg/24 hours during the 48-week double blind treatment phase.

The ability of the Exelon Patch 13.3 mg/24 hours to improve cognitive performance over that provided by the Exelon Patch 9.5 mg/24 hours was assessed by the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) [see International 24-Week Study *(14.1)*].

The ability of the Exelon Patch 13.3 mg/24 hours to improve overall function versus that provided by Exelon Patch 9.5 mg/24 hours was assessed by the instrumental sub-scale of the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-IADL). The ADCS-IADL sub-scale is composed of items 7 to 23 of the caregiver-based ADCS-ADL scale. The ADCS-IADL assesses activities such as those necessary for communicating and interacting with other people, maintaining a household, and conducting hobbies and interests. A sum score is calculated by adding the scores of the individual items and can range from 0 to 56, with higher scores indicating less impairment.

Out of a total of 1584 patients enrolled in the initial open-label phase of the study, 567 patients were classified as decliners and were randomized into the 48-week double-blind treatment phase of the study. Two hundred eighty-seven (287) patients entered the 9.5 mg/24 hours Exelon Patch treatment group and 280 patients entered the 13.3 mg/24 hours Exelon Patch treatment group.

Figure 5 illustrates the time course for the mean change from double-blind baseline in ADCS-IADL scores for each treatment group over the course of the 48-week treatment phase of the study. Decline in the mean ADCS-IADL score from the double-blind baseline for the Intent to Treat – Last Observation Carried Forward (ITT-LOCF) analysis was less at each timepoint in the 13.3 mg/24 hour Exelon Patch treatment group than in the 9.5 mg/24 hours Exelon Patch treatment group. The between-treatment group differences for Exelon Patch 13.3 mg/24hours versus Exelon Patch 9.5 mg/24 hours were statistically significant at weeks 16, 24, 32 and 48 (primary endpoint).

Figure 6 illustrates the time course for the mean change from double-blind baseline in ADAS-Cog scores for both treatment groups over the 48-week treatment phase. The between-treatment group difference for Exelon Patch 13.3 mg/24 hours versus Exelon Patch 9.5 mg/24 hours was nominally statistically significant at week 24 (p=0.027), but not at week 48 (p=0.227), which was the primary endpoint.

Figure 5 Time Course of the Change from Double-Blind Baseline in ADCS-IADL Score for Patients Observed at Each Time Point in Study 2

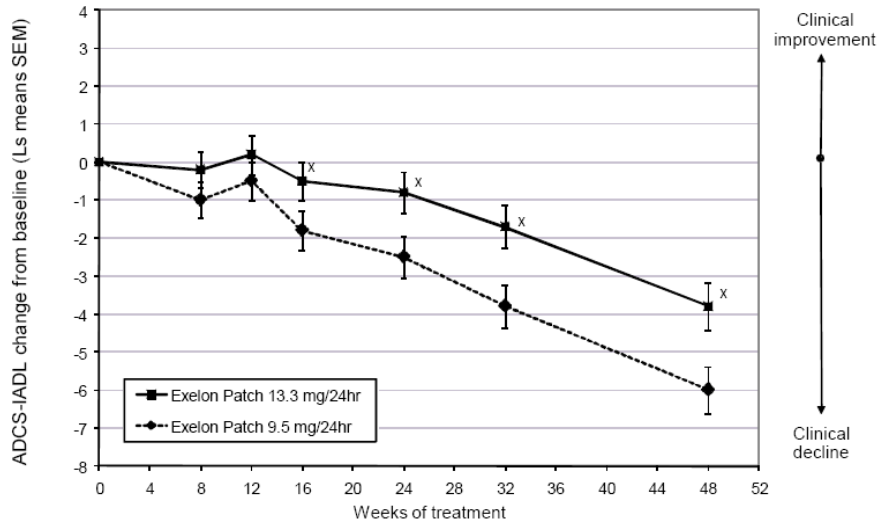
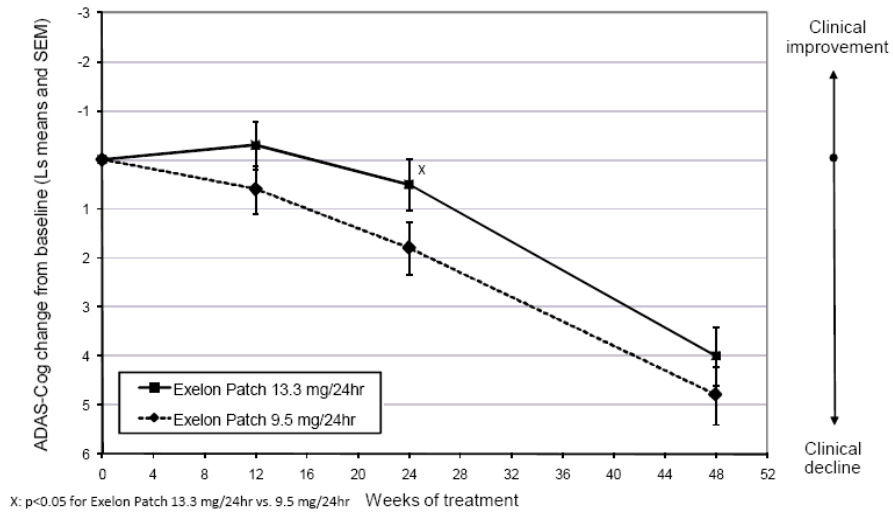


Figure 6 Time Course of the Change from Double-Blind Baseline in ADAS-Cog Score for Patients Observed at Each Time Point in Study 2



16 HOW SUPPLIED/STORAGE AND HANDLING

Exelon Patch: 4.6 mg/24 hours

Each patch of 5 cm^2 contains 9 mg rivastigmine base with *in vivo* release rate of 4.6 mg/24 hours.

Carton of 30……NDC 0078-0501-15

Exelon Patch: 9.5 mg/24 hours

Each patch of 10 cm^2 contains 18 mg rivastigmine base with *in vivo* release rate of 9.5 mg/24 hours.

Carton of 30……..NDC 0078-0502-15

Exelon Patch: 13.3 mg/24 hours

Each patch of 15 cm^2 contains 27 mg of rivastigmine base with *in-vivo* release rate of 13.3 mg/24 hours.

Carton of 30……..NDC 0078-0503-15

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep Exelon Patch in the individual sealed pouch until use. Each pouch contains one patch. Used systems should be folded, with the adhesive surfaces pressed together, and discarded safely.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information).

Importance of Correct Usage

Inform patients or caregivers of the importance of applying the correct dose on the correct part of the body. They should be instructed to rotate the application site in order to minimize skin irritation. The same site should not be used within 14 days. The previous day's patch must be removed before applying a new patch to a different skin location. Exelon Patch should be replaced every 24 hours and the time of day should be consistent. It may be helpful for this to be part of a daily routine, such as the daily bath or shower.

Instruct patients or caregivers to avoid exposure of the patch to external heat sources (excessive sunlight, saunas, solariums) for long periods of time.

Instruct patients who have missed a dose to apply a new patch immediately. They may apply the next patch at the usual time the next day. Instruct patients to not apply two patches to make up for one missed.

Inform the patient or caregiver to contact the physician for retitration instructions if treatment has been interrupted.

Discarding Used Patches

Instruct patients or caregivers to fold the patch in half after use, return the used patch to its original pouch, and discard it out of the reach and sight of children and pets. They should also be informed that drug still remains in the patch after 24-hour usage. They should be instructed to avoid eye contact and to wash their hands after handling the patch.

Gastrointestinal Adverse Reactions

Inform patients or caregivers of the potential gastrointestinal adverse reactions such as nausea, vomiting, and diarrhea, including the possibility of dehydration due to these symptoms. Explain that Exelon Patch may affect the patient's appetite and/or the patient's weight. Patients and caregivers should be instructed to look for these adverse reactions, in particular when treatment is initiated or the dose is increased. Instruct patients and caregivers to inform a physician if these adverse reactions persist.

Concomitant Use of Drugs with Cholinergic Action

Inform patients or caregivers that while wearing Exelon Patch, patients should not be taking Exelon capsules or Exelon oral solution or other drugs with cholinergic effects.

PATIENT INFORMATION

Exelon Patch *[ECS-'el-on]*

(rivastigmine transdermal system)

Exelon Patch is for skin use only.

Read this Patient Information leaflet before you start using Exelon Patch and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment. If you do not understand the information, or have any questions about Exelon Patch, talk with your healthcare provider or pharmacist.

Exelon patch is available in 3 dosage strengths

- 4.6 mg per day (4.6 mg/24 hours)

- 9.5 mg per day (9.5 mg/24 hours)
- 13.3 mg per day (13.3 mg/24 hours)

What is Exelon Patch?

Exelon Patch is a prescription medicine used to treat:

- mild to moderate memory problems (dementia) associated with Alzheimer's disease.
- mild to moderate memory problems (dementia) associated with Parkinson's disease.

It is not known if Exelon Patch is safe or effective in children.

Who should not use Exelon Patch?

Do not use Exelon Patch if you are allergic to rivastigmine, carbamate derivatives, or any of the ingredients in Exelon Patch. See the end of this leaflet for a complete list of ingredients in Exelon Patch.

Ask your healthcare provider if you are not sure.

What should I tell my healthcare provider before using Exelon Patch?

Before you use Exelon Patch, tell your healthcare provider if you:

- have or ever had a stomach ulcer
- are planning to have surgery
- have or ever had problems with your heart
- have problems passing urine
- have or ever had seizures
- have problems with movement (tremors)
- have asthma or breathing problems
- have a loss of appetite or are losing weight
- are pregnant or plan to become pregnant. It is not known if Exelon Patch will harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if Exelon Patch passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you use Exelon Patch.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take:

- a medicine used to treat inflammation (nonsteroidal anti-inflammatory drugs)
- other medicines used to treat Alzheimer's or Parkinson's disease
- an anticholinergic medicine, such as an allergy or cold medicine, a medicine to treat bladder or bowel spasms, or certain asthma medicines, or certain medicines to prevent motion or travel sickness

Ask your healthcare provider if you are not sure if your medicine is one listed above.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How should I use Exelon Patch?

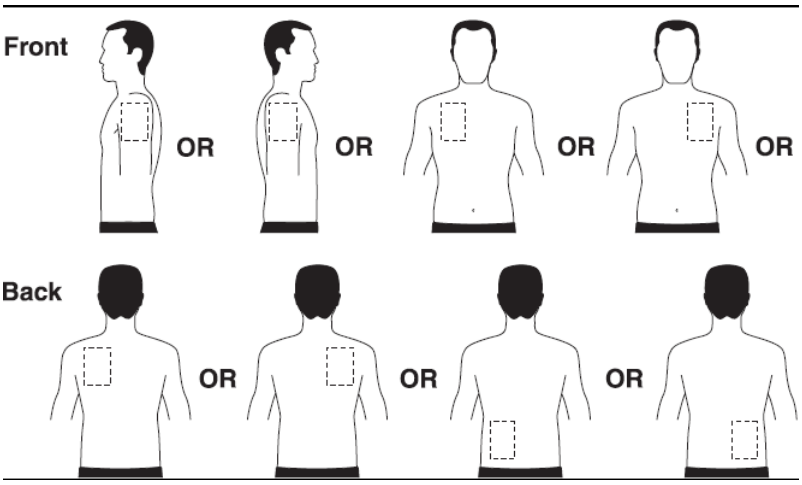
- Use Exelon Patch exactly as your healthcare provider tells you to use it.
- Your healthcare provider may change your dose as needed.
- Wear only 1 Exelon Patch at a time.
- Exelon Patch is for skin use only.
- Apply Exelon Patch to clean, dry, hairless, intact skin.
- Avoid applying Exelon Patch to areas on your body that will be rubbed against tight clothing.
- Do not apply Exelon Patch to skin that is red, irritated, or has cuts.
- Do not apply Exelon Patch to skin that has cream, lotion, or powder on it.
- Change your Exelon Patch every 24 hours at the same time of day. You may write the date and time you put on the Exelon Patch with a ballpoint pen before applying the patch to help you remember when to remove it.
- Change your application site every day to avoid skin irritation. You can use the same area, but do not use the same spot for at least 14 days after your last application.
- Check to see if the patch is loosened when engaging in activities such as bathing, swimming, or showering.
- If your Exelon Patch falls off, put on another patch right away and then replace the new patch the next day at the same time as usual. Do not use overlays, bandages, or tape to secure patches that have loosened or reapply patches that have fallen off.
- If you miss a dose or forget to change your Exelon Patch apply your next Exelon Patch as soon as you remember. Do not apply 2 Exelon Patches to make up for the missed dose.
- If you miss more than three days of applying Exelon Patch, call your healthcare provider before putting on another patch.
- You must remove Exelon Patch from the previous day *before* applying a new one.
- **Having more than one patch on your body at the same time can cause you to get too much Exelon. If you accidentally use more than one Exelon Patch at a time call your healthcare provider. If you are unable to reach your healthcare provider, contact your local Poison Control Center or go to the nearest hospital emergency room right away.**

Where should I Apply Exelon Patch?

- Apply 1 Exelon Patch to **ONLY ONE** of the outlined areas shown in the figures below (See figure A):
    - upper back, left or right side
    - lower back, left or right side
    - upper arm, left or right
    - chest, left or right side

Figure A

Apply one patch to ONLY ONE of the following possible sites each day



The diagram represents areas on the body where Exelon Patch may be applied. Only one patch should be worn at a time. Do not apply multiple patches to the body.

Apply **ONLY ONE** patch per day to **ONLY ONE** of the following locations (as illustrated above): the upper **or** lower back if it is likely that the patient will remove it. If this is not a concern, the patch can be applied **instead** to the upper arm **or** chest. Avoid places where the patch can be rubbed off by tight clothing.

Apply Exelon Patch as follows:

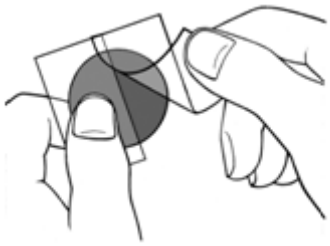
The patch is a thin, beige, plastic patch that sticks to the skin. Each patch is sealed in a pouch that protects it until you are ready to put it on. Do not open the pouch or remove a patch until just before you apply it.

1. Cut the pouch along the dotted line to open and remove the patch (See Figure B). Save the pouch for later use. **The patch should not be cut or folded sharply.**

Figure B

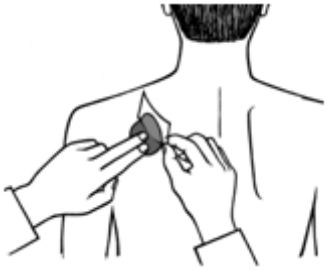
2. A protective liner covers the sticky (adhesive) side of the patch. Peel off one side of the protective cover. Do not touch the sticky part of the patch with your finger (See Figure C).

Figure C



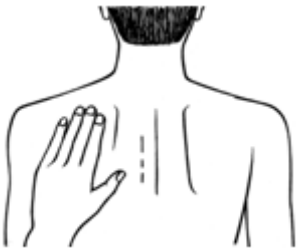
3. Apply the sticky side of the patch onto your chosen skin site.
4. Peel off the other side of the protective cover (See Figure D).

Figure D



5. Press down on the patch firmly to make sure that the edges stick well (See Figure E).

Figure E



Wash your hands with soap and water after applying the patch.

Removing the Exelon Patch:

- Gently pull on 1 edge of the Exelon Patch to remove it off your skin.
- Fold the Exelon Patch in half and put it back into the pouch that you saved.
- Throw the used Exelon Patch in the trash out of the reach of children and pets.
- Wash your hands with soap and water right away.

What should I avoid while using Exelon Patch?

- Do not touch your eyes after you touch the Exelon Patch.
- Exelon Patch can cause drowsiness, dizziness, weakness, or fainting. Do not drive, operate heavy machinery, or do other dangerous activities until you know how Exelon Patch affects you.
- Avoid exposure to external heat sources such as excessive sunlight, saunas, or solariums for long periods of time.

What are the possible side effects of Exelon Patch?

Exelon Patch may cause serious side effects including:

- **Stomach or bowel (intestinal) problems**, including:
  - nausea
  - vomiting
  - diarrhea
  - dehydration
  - loss of appetite
  - weight loss
  - bleeding in your stomach (ulcers)
- **heart problems**
- **seizures**
- **problems with movement (tremors)**

The most common side effects of Exelon Patch include:

- depression
- headache
- anxiety
- dizziness
- stomach pain
- urinary tract infections
- muscle weakness
- tiredness
- trouble sleeping

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Exelon Patch. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store Exelon Patch?

- Store Exelon Patch at 59°F to 86°F (15°C to 30°C).
- Keep Exelon Patch in the sealed pouch until ready to use.

Keep Exelon Patch and all medicines out of the reach of children.

General information about the safe and effective use of Exelon Patch.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use Exelon Patch for a condition for which it was not prescribed. Do not give Exelon Patch to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about Exelon Patch. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Exelon Patch that is written for health professionals.

What are the ingredients of Exelon Patch?

Active ingredient: rivastigmine

Distributed by:

Novartis Pharmaceuticals Corporation

East Hanover, New Jersey 07936

T2012-XXX/T2012-XXX
August 2012/August 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

OFFICE DIRECTOR MEMO

MEMORANDUM

DATE: August 19, 2012

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22083/S-016

SUBJECT: Action Memo for NDA 22083/S-016, for the approval of Exelon Patch (rivastigmine transdermal system) 13.3 mg/24 hours

NDA 22083/S-016, for the approval of Exelon Patch (rivastigmine transdermal system) 13.3 mg/24 hours (15 cm^2), was submitted by Novartis Pharmaceuticals Corporation on 10/31/11. Exelon Patch (5 and10 cm^2, delivering 4.6 mg/24 hours and 9.5 mg/24 hours, respectively) is currently approved for the treatment of mild to moderate Alzheimer's Disease (AD) and mild to moderate dementia associated with Parkinson's Disease (PD). The 5 cm^2 patch is approved primarily for use during titration to the 10 cm^2 patch, and also is recommended for patients with renal or hepatic disease.

The current application contains the results of a single controlled trial, Study 2340, in which the10 and 15 cm^2 were compared in patients with mild to moderate AD, the goal of which was to demonstrate superiority of the latter on a cognitive and a global measure, the standard set of outcome measures used to assess the effectiveness of treatments for AD.

The application has been reviewed by Dr. Nicholas Kozauer, medical reviewer; Dr. Julia Luan, statistician; Jung Lee, Division of Medication Error Prevention and Analysis (DMEPA); Dr, Reema Mehta, Division of Risk Management; Dr. Zedong Dong, Office of New Drug Quality and Assessment (ONDQA); Dr. Antoine El Hage, Office of Scientific Investigation; and Dr. Ranjit Mani, neurology team leader and Cross-Discipline Team Leader (CDTL). Drs. Kozauer and Mani recommend that the application be approved; Dr. Luan has concluded that the sponsor has not submitted substantial evidence of effectiveness for the 15 cm^2 patch.

I will briefly review the relevant results of Study 2340, and offer the rationale for the division's action.

Study 2340

This was a double blind trial in which patients previously treated for 48 weeks with open-label Exelon Patch 10 cm^2, and whose AD progressed, were randomized to continue on that dose, or receive Exelon Patch 15 cm^2 for an

additional 48 weeks. The co-primary outcomes were the mean change from double-blind baseline at Week 48 in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), and the Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-IADL), two standard measures of drug effect in studies of AD treatments (the scales are described in detail by Dr. Kozauer). Secondary outcome measures included:

1) Time to Functional Decline-based on specified changes on the ADCS-IADL
2) Trail Making Tests (Parts A and B)
3) Neuropsychiatric Inventory (NPI)
4) Mini-Mental State Examination (MMSE)

The following rule was applied to a patient's course in the open-label phase to determine their eligibility for the double-blind portion of the study:

A decline in MMSE of at least 2 points from the last visit, or a decline of at least 3 points from the open-label baseline.

The primary analysis was to be an Analysis of Covariance (ANCOVA), based on the intent-to-treat last observation carried forward (ITT-LOCF) population. Other analyses to be done included a per-protocol analysis of observed cases and a per-protocol analysis using last observation carried forward.

The study was powered to detect a treatment difference of 1.9 points on both the ADAS-cog and ADCS-IADL scores with 85% power; this resulted in a sample size calculation of 410 patients/group.

Results

The study was performed in seven countries: US, Canada, Germany, Spain, France, Switzerland, and Italy.

A total of 1584 patients enrolled in the open-label phase. The following chart displays the number of patients in various populations in the double-blind phase:

	15 cm patch	10 cm patch
Randomized	280	287
Intent-to-treat	265	271
Per-protocol	194	214
Observed Cases	211	193

About 40% of the patients in the 15 cm patch group (104/265) were enrolled in the US.

The following charts display the results of the analyses of both co-primary

outcomes for the ITT-LOCF populations (the results on other analyses are similar):

ADAS-cog; Mean Change from Baseline

	Exelon 15 cm		Exelon 10 cm		P-value
	N	Change	N	Change	
Week 12	264	-0.2	268	0.6	0.09
Week 24	264	1.0	268	2.2	0.03
Week 48	264	4.1	268	4.9	0.23

ADCS-IADL; Mean Change from Baseline

	Exelon 15 cm		Exelon 10 cm		P-value
	N	Change	N	Change	
Week 8	265	-0.2	271	-0.8	0.11
Week 12	265	0.1	268	-0.4	0.25
Week 16	265	-0.7	268	-1.8	0.025
Week 24	265	-1.5	268	-2.8	0.005
Week 32	265	-2.2	268	-4.0	<0.001
Week 48	265	-4.4	268	-6.2	0.002

There were no statistically significant between-treatment contrasts on any of the secondary outcomes.

The following results are presented by country:

Treatment Differences by Country

ADAS-cog

Country	Total N	Treatment Difference
US	205	-1.47
Italy	111	0.60
Germany	70	-4.52
Canada	66	0.23
France	50	2.15
Spain	17	-4.27
Switzerland	13	6.26

ADCS-IADL

Country	Total N	Treatment Difference
US	206	3.48
Italy	112	0.19
Germany	72	3.21
Canada	66	-2.03
France	50	1.24
Spain	17	2.96
Switzerland	13	3.17

Safety

Deaths

As described by Dr. Kozauer, there were 3 deaths (1.1%) in the 15 cm group compared to 5 (1.8%) in the 10 cm group. In the 15 cm group, one death (a 61 year old man who died of aspiration pneumonia after about 2 ½ months of treatment at the higher dose) was possibly related to treatment, though he had a complicated clinical course. It is also worth noting that 2/5 deaths in the 10 cm patch group also were related to respiratory causes.

Serious adverse events (SAEs)

Although the overall rate of SAEs was comparable between the groups, there was an increase in the incidence of pneumonia (1.4% vs 0.7%) in the 15 cm group compared to the 10 cm group.

Adverse events leading to discontinuation

The following chart displays the adverse events leading to discontinuation that were more frequent in the 15 cm compared to the 10 cm group:

Event	Exelon 15 cm (N)		Exelon 10 cm (N)	
Vomiting	(5)	1.8%	(1)	0.35%
Pneumonia	(2)	0.7%	(1)	0.35%
Dehydration	(2)	0.7%	(0)	0%
Dizziness	(2)	0.7%	(0)	0%

It is worth noting that there were numerous adverse events leading to discontinuation that occurred at a higher frequency in the 10 cm group compared to the 15 cm group (see, for example, Dr. Kozauer's Table, Section 5.3.1.13.5.3.2.3,page 62-64 of his review).

Common adverse events

The adverse events of interest that occurred more frequently in the 15 cm group compared to the 10 cm group primarily involved the gastrointestinal (GI) tract, and are listed below:

Event	Exelon 15 cm (N)		Exelon 10 cm (N)	
Nausea	(42	15%	(19)	7%
Vomiting	(36)	13%	(22)	8%
Weight decreased	(25)	9%	(18)	6%
Decreased appetite	(22)	8%	(12)	4%
Abdominal pain	(21)	8%	(11)	4%
Insomnia	(19)	7%	(11)	4%

Comments

The sponsor has presented the results of a single randomized controlled trial comparing Exelon 15 cm patch to Exelon 10 cm patch in patients with mild to moderate AD whose AD had progressed during open-label treatment with the 10 cm patch. The primary outcomes, mean change in ADAS-cog and ADCS-IADL, standard instruments used to assess the effects of treatments for AD, were to be assessed at Week 48.

As we have seen, there was a statistically significant between-treatment difference at Week 48 in the ADCS-IADL, but not on the ADAS-cog. For this

reason, as noted by Drs. Kozauer, Mani, and Luan, the study did not meet its protocol-specified criteria for declaring the study "positive". However, both Drs. Mani and Kozauer recommend that the application should be approved.

Clearly, the primary issue to be addressed in considering whether or not the application can be approved is the meaning of the lack of statistical significance between the treatments on the ADAS-cog at Week 48. Regarding this finding, Dr. Kozauer presents several arguments in favor of approval.

First among these is the fact that the study did not include a placebo group. That is, the study did not demonstrate that there is no effect of the 15 cm patch at Week 48 (where no effect is defined, as is typically the case, as no difference from placebo). Instead, the study failed to demonstrate statistical superiority to the 10 cm patch at Week 48 (though it did demonstrate numerical superiority). This finding can reasonably be interpreted as being consistent with the following two conclusions (though, of course, it does not conclusively establish either one): either both the 15 and 10 cm patches are not different from placebo after 48 weeks of treatment, or there is no (material) difference between the two treatments at Week 48 (at least in this study). The former interpretation is interesting, but it is of little regulatory import. That is, as has been noted clearly by Dr. Kozauer, previous treatments for AD have been approved on the basis of studies of between 12-24 weeks; no studies of these treatments have been longer than 24 weeks. For this reason, we have no information about whether or not the effects seen at 12-24 weeks persist beyond that time. Of course, we hope that they do, but no controlled trials address the question. And it is clear that the lack of a statistically significant difference between the 15 cm and 10 cm patches seen in Study 2340 will not be the basis for considering removing the 10 cm patch from the market, because, we have previously established that the 10 cm patch is effective out to 24 weeks. Therefore, the finding of no statistically significant difference between the treatments at Week 48 does not argue against approving the 15 cm patch (because it is no worse than the 10 cm patch at that time point, even if we interpret this specific trial as being consistent with neither having a positive effect on this outcome after 48 weeks of treatment).

However, there is positive evidence that there is a potential benefit to be had at Week 48 from the 15 cm patch, and that is the statistically significant superiority of the 15 cm patch compared to the 10 cm patch at Week 48 on the ADCS-IADL. Even if we consider the possibility that the 10 cm patch has absolutely no effect on the ADCS-IADL at Week 48, this study establishes that the 15 cm patch does.

Dr. Kozauer points out that a statistically significant effect of the 15 cm patch has been established at Week 24 on the ADAS-cog. Again, this is not merely an effect compared to placebo; this is a finding which ostensibly establishes that the 15 cm patch is superior to the 10 cm patch, which is known to be effective on the ADAS-cog at that time point. What are we to make of this?

Can we fairly conclude that this study has established the statistically superiority of the 15 cm patch to the 10 cm patch at Week 24?

By the usual rules of study interpretation, I believe that we cannot. Specifically, given the failure of the 15 cm patch to be superior to the 10 cm patch at Week 48 on the ADAS-cog, we are not permitted to even perform a statistical test of the difference between the treatments at any other time point. Such a comparison may produce, as noted by Dr. Mani, a "nominally" significant between-treatment contrast (as it has here), but the interpretation of such a nominally significant p-value is difficult to understand. For this reason, I do not believe that we can consider the difference seen between the treatments at Week 24 to be statistically significant, as that term is commonly understood.

However, there are other considerations.

As Dr. Kozauer describes, there is precedent for approving higher doses than previously approved lower doses of various AD treatments in the face of a lack of statistical significance between the doses on at least one co-primary outcome. He cites the cases of Aricept 5 and 10 mgs, as well as the recent approval of Aricept 23 mg, which did not show statistical superiority compared to the 10 mg dose on the CIBIC+, the co-primary measure of global functioning. This latter case is particularly relevant here, given that the study that compared the two doses did not include a placebo group. Indeed, it is not uncommon for a higher dose of many treatments to be recommended for some patients if that higher dose has been shown to be numerically, though not necessarily statistically, superior to a lower dose, when we have assurance that that lower dose is effective, and the higher dose has been shown to be acceptably safe.

The case here is further complicated by the fact, previously mentioned, that this study was 48 weeks long, and that we have no previous experience with studies of this duration. In other words, we have (and had at the time that the protocol was being discussed with the sponsor) no way to understand what the expectations for the duration of any treatment effect would be. There have been cases, in my experience, where a sponsor has chosen an outcome measure that, after the fact, the Agency judged as being inappropriate for the clinical situation being studied, and, for that reason, chose to analyze as primary (even though the study as analyzed by protocol was negative) an alternative, more reasonable outcome. This is somewhat similar to a scenario in which the assumptions supporting a protocol-specified statistical analysis are not met (e.g., the data are not normally distributed), and an alternative analysis must be performed, even though it was not prospectively designated. Given our lack of experience with studies longer than 24 weeks, one could imagine that we could choose to rely on the outcome at a time more appropriate than the one chosen by protocol, one more appropriate based on our experience (although I acknowledge that one could argue that an analysis at 12 weeks-a time in this trial where there was not statistically significant superiority of the 15 cm patch compared to the 10 cm

patch-could also be chosen based on previous experience). Although this is a possibility, I think it would be hard to justify (especially when we could reasonably choose Week 12 instead of Week 24, a time where there was no statistically significant difference between the treatments on ADAS-cog).

Dr. Kozauer makes the reasonable point that the lack of statistical significance between treatments on the ADAS-cog at Week 24 may have been related to the large number of dropouts (indeed, as noted above, about 20% and 29% of the 15 cm and 10 cm patients, respectively, did not complete the study). The results of the OC analysis on the ADAS-cog did yield a somewhat smaller p-value than the primary LOCF analysis (0.14 vs 0.23) and a larger estimate of the treatment effect (-1.2 vs -0.8), but clearly this analysis did not yield a significant difference.

Despite these several misgivings, however, I do believe we can approve the 15 cm patch, primarily because the data clearly, in my view, establish clear numerical superiority of the 15 cm patch compared to the 10 mg patch for at least 24 weeks on the ADAS-cog (a reasonable time point at which to assess treatments for AD), and clear statistically significant superiority out to 48 weeks on the ADCS-IADL, an important measure of overall patient functioning (it is also worth noting that far fewer patients were enrolled than were planned for; this could also have affected the study's ability to detect a statistically significant treatment difference). These findings are of particular meaning because they were seen in patients who were failing to continue to respond to the lower dose. Findings of this sort, as pointed out clearly by Dr. Kozauer, have been relied upon in the past to approve higher doses of previously approved lower doses for many drugs, as long as we can conclude that the safety profile of those higher doses is acceptable. This latter is clearly the case here (indeed, as Dr. Kozauer has pointed out, even though there are some increases in adverse events at the 15 cm patch compared to the 10 cm patch-notably for vomiting-the incidence of these events at the higher dose are still substantially less than the incidence of these events seen with the approved doses of the oral products).

Finally, Dr. Dong notes that the sponsor has made changes to the release liner, which they previously described in the 2010 Annual Report. Although he has found that the new release liner is acceptable, (b) (4)

For these reasons, then, I will issue the attached approval letter, with appended agreed-upon product labeling.

Russell Katz, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
08/31/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	8/31/12
From	Ranjit B. Mani, MD
Subject	Cross-Discipline Team Leader Review Division of Neurology Products
NDA/BLA # **Serial #**	22083 046
Applicant	Novartis
Date of Submission	10/28/11
PDUFA Goal Date	8/31/12
Proprietary Name / Established (USAN) names	Exelon® Patch (rivastigmine transdermal system)
Dosage forms / Strength	15 cm^2 patch size (13.3 mg/24 hours nominal release rate; 27 mg total drug load)
Proposed Indication(s)	1. Mild to moderate dementia of the Alzheimer's type 2. Mild to moderate dementia associated with Parkinson's Disease
Recommendation	Approval

1 Introduction

This Supplemental New Drug Application (NDA) seeks the approval of a new (higher) strength formulation of the Exelon® Patch (rivastigmine transdermal system) for the treatment of both mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's Disease.

Exelon® (rivastigmine tartrate) is an acetylcholinesterase inhibitor drug initially approved by this Agency on April 21, 2000, as immediate-release capsule and oral solution formulations, for the treatment of mild to moderate dementia of the Alzheimer's type. The immediate-release capsule and oral solution formulations of Exelon® were also approved by this Agency for the treatment of mild to moderate dementia associated with Parkinson's Disease on June 27, 2006. Both approvals were under NDA 20823.

A transdermal formulation of rivastigmine, the Exelon® Patch (rivastigmine transdermal system) was approved for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's Disease on July 6, 2007, under NDA 22083 (the application was originally submitted on September 8, 2006). The transdermal formulation strengths then approved were as displayed in the table below; these strengths of the Exelon® Patch continue to be marketed in this country for both indications.

Exelon® Patch Size	**Rivastigmine Nominal Dose**	**Rivastigmine Content Per Patch**
5 cm^2	4.6 mg/24 hours	9 mg
10 cm^2	9.5 mg/24 hours	18 mg

In the application under NDA 22083 that led to the Agency's action described immediately above, (b) (4)

(b) (4)

The sponsor is now (b) (4) seeking the approval of the same 15 cm^2 Exelon® Patch (rivastigmine nominal dose of 13.3 mg/24 hours; rivastigmine content per patch of 27 mg) (b) (4). The indication for which the sponsor is now seeking the approval of the 15 cm Exelon® Patch is (b) (4) for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's Disease.

2 Background

The new data contained in this submission, which also form the core basis for the current application, are those of a single randomized, double-blind, placebo-controlled, parallel-arm study ENA713D2340, also referred to as Study D2340, which was conducted in patients with mild to moderate Alzheimer's Disease; there were no additional new clinical studies whose data are included in this submission.

The design of Study D2340 which is further described later in this review was discussed with the sponsor at an End-of-Phase 2 meeting that was held on November 24, 2008. The summary results of Study D2340 were then discussed with the sponsor at a Pre-sNDA meeting held on August 8, 2011. The key agreements reached at both meetings are outlined later in this review.

The earlier approval of the Exelon® Patch in 5 cm^2 and 10 cm^2 strengths for the treatment of both mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's Disease was also based on a single randomized, double-blind, placebo-controlled, parallel-arm study conducted in patients with mild to moderate Alzheimer's Disease alone; this was Study ENA713D2320, also referred to as Study D2320. As will be clear later in this review, are significant differences in design between Study D2320 and Study D2340.

3 Chemistry, Manufacturing, And Controls

The primary Chemistry review of this submission was completed by Zedong Dong, PhD, on August 30, 2012.

Dr Dong notes that the Chemistry, Manufacturing, and Controls data for the proposed new dosage strength (15 cm^2) of the Exelon® Patch [redacted] (b) (4) aspects of the 15 cm^2 Exelon® Patch [redacted] (b) (4) were addressed during the review of the current application, as follows.

- [redacted] (b) (4) specifications for the 15 cm^2 Exelon® Patch were provided by the sponsor to the Agency's satisfaction after discussions between the Agency and sponsor
- A change in release liner (from [redacted] (b) (4)) for the proposed 15 cm^2 Exelon® Patch (and for the approved 5 cm and 10 cm Exelon® Patches) was the subject of new data submitted during the period of review at the Agency's request and is also to be the [redacted] (b) (4) (as agreed upon during discussions between the Agency and sponsor).

Dr Dong notes that the Product Quality Microbiology Reviewer has concluded that there were no quality microbiological concerns for this supplement based on the information provided. He further observes that the Biopharmaceutics Reviewer (see below) has recommended approval of this application.

Dr Dong has concluded that the current application may be approved.

4 Biopharmaceutics

The primary Biopharmaceutics review of this application was completed by Tapash K Ghosh, PhD, on August 30, 2012.

Dr Ghosh's review was primarily directed at determining the acceptability of the comparative *in vitro* release profiles and similarity f2 data provided for two manufacturing facilities: the LTS Lohmann Therapy Systems site in West Caldwell, New Jersey, USA; and the Lohmann Therapie Systeme AG site in Andernach, Rhineland-Palatinate, Germany. The Exelon® Patch strengths used in Study D2340 and the 15 cm^2 Exelon® Patch for which pharmacokinetic data were included in the original submission under NDA 22083 (and used to support the current application) were all manufactured at the facility in Andernach, Germany.

Dr Ghosh has concluded from the data provided by the sponsor that the dissolution profiles of the 15 cm^2 Exelon® Patch manufactured at each of the aforementioned sites are similar. He has recommended that the current application be approved.

5 Clinical Pharmacology

The primary Clinical Pharmacology review of this submission was completed by Jagan Parepally, PhD, on August 8, 2012.

Dr Parepally notes that the clinical pharmacology of the proposed new dosage strength (15 cm^2) of the Exelon® Patch was fully characterized [redacted] (b) (4) o new clinical pharmacology studies were conducted with the 15 cm Exelon® Patch in support of the current application.

Dr Parepally further notes that the sponsor has conducted an *in vitro* study of the potential for rivastigmine and its main metabolite NAP226-90 to inhibit CYP2B6: the study indicates that neither rivastigmine nor NAP226-90 has the potential to inhibit CYP2B6 *in vivo*.

6 Clinical Efficacy And Safety

The primary clinical review of this application was completed by Nicholas Kozauer, MD, on July 17, 2012. Please see his review for full details of the clinical efficacy and safety data included in this submission.

I have summarized the clinical efficacy and safety data in this application below.

6.1 Design And Efficacy Results Of Study D2340

6.1.1 Design Of Study D2340

As already noted, the results of Study D2340 are the core basis for the current application.

Study D2340 consisted of the following consecutive phases

1. A 48-week initial open-label phase where all patients received the approved 10 cm^2 Exelon® Patch (after a beginning 4-week titration phase where all subjects received the approved 5 cm^2 patch). Patients who declined clinically – as manifest by a decline in Mini-Mental Status Examination score of <u>either</u> ≥ 2 points from an earlier visit <u>or</u> of ≥ 3 points from the baseline of the initial open-label phase during this phase were to be enrolled in the subsequent open-label phase .

2. A 48-week double-blind, parallel-arm treatment phase at entry to which patients were to be randomized to treatment with either the 10 cm^2 Exelon® Patch (i.e., continuing the same dose as in the initial open-label phase) or the 15 cm^2 Exelon® Patch.

The main criteria for entry into Study D2340 was the diagnosis of Probable Alzheimer's Disease, according to the NINCDS-ADRDA criteria, (and a diagnosis of dementia of the Alzheimer's type according to the DSM-IV criteria) and a Mini-Mental

Status Examination score at entry into the study that ranged from 10 to 24, inclusive (this range is representative of a mild to moderate severity of Alzheimer's Disease).

The objective of this study was, therefore, to determine if the 15 cm^2 Exelon® Patch could be of more benefit than continuing the 10 cm^2 Exelon® Patch in patients with mild to moderate Alzheimer's Disease who had demonstrated a pre-specified cognitive decline while already using the 10 cm^2 Exelon® Patch.

The protocol-specified co-primary efficacy parameters were the change from baseline to Week 48 during the double-blind phase in the total Alzheimer's Disease Assessment Scale – Cognitive (ADAS-Cog) and in the instrumental Alzheimer's Disease Cooperative Study – Activities of Daily Living Scale (ADCS-ADL) score. Note that the instrumental ADCS-ADL is a subset of the full ADCS-ADL. The primary efficacy analysis was to be performed using the intent-to-treat population, consisting of all patients who were randomized, received at least one dose of study medication during the double-blind phase and had at least one post-randomization assessment of the primary efficacy parameter being analyzed. During the primary efficacy analysis, the treatment groups were to be compared using least squares means derived from an analysis of covariance model with the following explanatory variables: treatment, country, and last test score. The last-observation-carried-forward method of imputation was to be used for this analysis. The 0.05 level of significance was to be used for the primary efficacy analysis.

Secondary efficacy measures included the time to decline in the ADCS-ADL (instrumental) during the double-blind phase, the Trailmaking Test Parts A and B, and the 10-item Neuropsychiatry Inventory.

Safety assessments included adverse events, vital signs, body weight, safety laboratory tests, and electrocardiograms.

6.1.2 Earlier Discussions With Sponsor Regarding Study D2340

The protocol for Study D2340 (similar to the current protocol in its broad design) was first discussed with the sponsor at the End-of-Phase 2 meeting that that was held with the Division on November 24, 2008. Among the key agreements reached at the meeting were the following:

- The protocol for Study D2340 should include a global or functional primary efficacy measure in addition to the ADAS-Cog, the sole stipulated primary efficacy measure
- The primary efficacy analysis in Study D2340 should be conducted in the intent-to-treat population, further defined as consisting of all subjects having at least a single post-baseline assessment for the both co-primary efficacy measures, using the last-observation-carried-forward method of imputation.
- A single study designed such as Study D2340 would support the approval of the 15 cm^2 Exelon® Patch assuming that the ADCS-ADL was also used as a co-primary

efficacy measure (the use of that instrument as a co-primary efficacy measure was proposed by the sponsor).

An explanation for why the sponsor had chosen a 48-week duration for the double-blind phase of Study D2340 was not provided to the Agency at the above End-of-Phase 2 meeting or subsequently.

The results of Study D2340, then available in outline form, were discussed at a Pre-SNDA meeting held on August 8, 2011. The following is a list of the main agreements reached at that meeting:

- The lack of a statistically significant difference between the 2 treatment groups on the change from baseline to Week 48 in ADAS-Cog total score (one of the 2 co-primary efficacy measures for the study) would not be a reason for a Refuse-to-File decision when the proposed SNDA was submitted.

- The results of Study D2340 bore a partial similarity to those of the single efficacy study that led to the approval of the 23 mg strength of Aricept® (donepezil hydrochloride) tablet for the treatment of moderate to severe Alzheimer's Disease; in the latter study, evidence for efficacy of the 23 mg dose over the comparator 10 mg dose of Aricept® was lacking on the Clinician Interview-Based Impression of Change-Plus (CIBIC-Plus), the global co-primary efficacy measure, but not on the ADAS-Cog (the cognitive co-primary efficacy measure). The sponsor of the current application was advised to address both the similarities and differences and differences that might exist between the results of the aforementioned two studies.

6.1.3 Efficacy Results Of Study D2340

The analyses whose results are described below are for the double-blind treatment phase only.

6.1.3.1 Patient Disposition

1584 patients were enrolled in the initial open-label phase of this study, with 567 patients later entering the double-blind treatment phase of the study.

Of the 567 patients entering the double-blind treatment phase, 280 patients were randomized to the Exelon® Patch 15 cm^2 treatment group and 287 patients to the Exelon® Patch 10 cm^2 treatment group (in the latter group, 286 patients actually received study drug). Key demographic and other baseline characteristics were comparable between the 2 treatment groups.

207 patients (73.9%) in the Exelon® Patch 15 cm^2 treatment group and 203 patients (70.7%) in the Exelon® Patch 10 cm^2 treatment group completed the double-blind treatment phase of the study.

6.1.3.2 Analysis Of Primary Efficacy Parameters

[The results described below are displayed graphically in the submission and in the Agency primary clinical review, but I have not reproduced those figures here].

6.1.3.2.1 ADAS-Cog

The analysis of the mean change from baseline in ADAS-Cog score, comparing the 2 treatment groups at Weeks 12, 24, and 48 is displayed in the following table. The analysis is based on the intent-to-treat population using the last-observation-carried-forward method of imputation and the analysis of covariance model described earlier.

Timepoint	Exelon® 15 cm^2		Exelon® 10 cm^2		Exelon® 15 cm^2 – Exelon® 10 cm^2		
	N	Mean change*	N	Mean change*	DLSM	95% CI	p-value
Week 12	264	-0.2	268	0.6	-0.9	(-2.0, 0.1)	0.091
Week 24	264	1.0	268	2.2	-1.3	(-2.5, 0.2)	0.027
Week 48	264	4.1	268	4.9	-0.8	(-2.1, 0.5)	0.227

* from baseline
DLSM: Difference in least squares means
CI: Confidence Interval

A broadly similar pattern of results was seen in the observed cases population.

As noted in the table above, the protocol-specific primary efficacy analysis of the ADAS-Cog (using the change from baseline to Week 48) did not achieve statistical significance and the effect size (as estimated by the difference in least squares means) was very small at all timepoints, albeit largest at Week 24 at which timepoint that effect was nominally statistically significant.

6.1.3.2.2 Instrumental ADCS-ADL

The analysis of the mean change from baseline in the instrumental ADCS-ADL score, comparing the 2 treatment groups at Weeks 12, 24, and 48 is displayed in the following table. The analysis is based on the intent-to-treat population using the last-observation-carried-forward method of imputation and the analysis of covariance model described earlier.

Timepoint	Exelon® 15 cm^2		Exelon® 10 cm^2		Exelon® 15 cm^2 – Exelon® 10 cm^2		
	N	Mean change*	N	Mean change*	DLSM	95% CI	p-value
Week 12	265	0.1	271	-0.4	0.7	(-0.5, 1.8)	0.252
Week 24	265	-1.5	271	-2.8	1.7	(0.5, 2.9)	0.005
Week 48	265	-4.4	271	-6.8	2.2	(0.8, 3.6)	0.002

* from baseline
DLSM: Difference in least squares means
CI: Confidence Interval

Again, a broadly similar pattern of results was seen in the observed cases population.

As also indicated in the above table the protocol-specified primary efficacy analysis did achieve statistical significance at Week 48, as well as nominal statistical significance at the earlier timepoint of Week 24.

6.1.3.3 Analysis Of Secondary Efficacy Measures

The analysis of these measures did not yield results that were even nominally statistically significant.

6.1.4 Safety Results Of Study D2340

All new safety data contained in this submission are derived from Study D2340.

The significant safety data in this application are those obtained from the randomized, double-blind latter phase of Study D2340. Within those data, special attention needs to be directed at the incidence of selected adverse events that are a reflection of cholinomimetic activity and have been of particular concern with acetylcholinesterase inhibitors as a class. These adverse events (by Preferred Term) include abdominal pain, decreased appetite, diarrhea, insomnia, nausea, vomiting, and weight decreased.

The number and proportion of patients in each treatment group with the above-listed selected adverse events occurring during the double blind phase of Study D2340 in are in the next table, which applies to the safety population. Note that the incidence of nausea and vomiting were clearly higher with a 15 cm^2 patch than with a 10 cm^2 patch.

Adverse Event (Preferred Term)	Exelon® 10 cm^2 (n = 283)	Exelon® 15 cm^2 (n = 280)
	N (%)	N (%)
Abdominal pain (all)	11 (3.9)	21 (7.6)
Decreased appetite	12 (4.2)	22 (7.9)
Diarrhea	25 (8.8)	25 (8.9)
Insomnia	11 (3.9)	19 (6.8)
Nausea	19 (6.7)	42 (15.0)
Vomiting	22 (7.8)	36 (12.9)
Weight decreased	18 (6.4)	25 (8.9)

The number and proportion of patients in each treatment group discontinuing study participation during the double-blind phase on account of the same selected adverse events is in the next table.

Adverse Event (Preferred Term)	Exelon® 10 cm^2 (n = 283)	Exelon® 15 cm^2 (n = 280)
	N (%)	N (%)
Abdominal pain (upper)	1 (0.4)	0 (0.0)
Decreased appetite	1 (0.4)	2 (0.7)
Diarrhea	1 (0.4)	0 (0.0)
Insomnia	1 (0.4)	0 (0.0)
Nausea	1 (0.4)	1 (0.4)
Vomiting	1 (0.4)	5 (1.8)
Weight decreased	0 (0.0)	1 (0.4)

The deaths and serious adverse events that occurred in this study are comparable in incidence and pattern between the treatment groups; none appear clearly attributable to study drug. Analysis of other safety measures, namely vital signs, electrocardiograms, and safety laboratory tests did not yield any findings of special concern.

6.2 Design And Efficacy Results Of Study D2320

As already noted, the earlier approval of the Exelon® Patch in 5 cm^2 and 10 cm^2 strengths for the treatment of both mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's Disease was also based on a single randomized, double-blind, placebo-controlled, parallel-arm study conducted in patients with mild to moderate Alzheimer's Disease alone; this was Study D2320 which was contained in the original submission under NDA 22083. When NDA 22083 was originally submitted, the sponsor had in fact (b) (4) strengths of Exelon® Patch for the aforementioned indications: 5 cm , 10 cm (b)

Note that the sponsor has not conducted a study of (any strength of) the Exelon® Patch in dementia associated with Parkinson's Disease. The earlier approval of the 5 cm^2 and 10 cm^2 strengths of the Exelon® Patch for that indication were based on the still-earlier approval of the oral formulations of Exelon® for the same indication based on a single efficacy study.

As the results of Study 2320 are at least somewhat relevant to the current application, I have appended a summary of that study below extracted from the corresponding clinical review, which was conducted by me.

6.2.1 Design

This was a randomized, double-blind, placebo-controlled, parallel-arm study of 24 weeks duration. The two key criteria used for enrolling patients in this study were a diagnosis of Probable Alzheimer's Disease by NINCDS-ADRDA criteria, and a Mini-Mental Status Examination entry score of 10-20.

Patients enrolled in this study were randomized to treatment with one of the following regimes for the 24-week period of double-blind, parallel-arm treatment, divided into a 16-week titration phase and an 8-week maintenance phase.

- Placebo
- Exelon® 10 cm^2 Patch QD (nominal rivastigmine release rate of 9.5 mg/24 hours)
- Exelon® 20 cm^2 Patch QD (nominal rivastigmine release rate of 17.4 mg/24 hours)
- Exelon® capsules 6 mg BID

While the assigned doses of Exelon® (patch or capsules) were to be achieved by titration, as already noted, doses below the target dose were permitted during the maintenance period in the event of poor tolerability.

The primary efficacy measures for the study were:

- ADAS-Cog
- The Alzheimer's Disease Cooperative Study – Clinical Global Impression Of Change (ADCS-CGIC)

Secondary efficacy measures included the Neuropsychiatry Inventory, Mini-Mental Status Examination, Ten-Point Clock Test, and Trailmaking Tests A and B. Safety measures included adverse events, vital signs, and electrocardiograms. Study outcome measures also included assessments of patch adhesion and skin irritation at the site of patch application.

The primary efficacy analysis involved evaluating the following two hypotheses in the same sequence as below.

1. The first hypothesis involved the comparison of the 20 cm^2 Exelon® Patch with placebo on both the ADAS-Cog and ADCS-CGIC. In order to demonstrate the superiority of the 20 cm^2 Exelon® patch over placebo, a statistically significant difference favoring placebo would need to be shown on both parameters. The testing sequence was to stop if the superiority of the 20 cm^2 Exelon® Patch over placebo could not be demonstrated
2. The second hypothesis involved the comparison of the 10 cm^2 Exelon® Patch with placebo on both the ADAS-Cog and ADCS-CGIC. In order to demonstrate the superiority of the 10 cm^2 Exelon® patch over placebo, a statistically significant difference favoring placebo would need to be shown on both parameters.

Since the study hypotheses were arranged in order *a priori*, and as both primary efficacy parameters were be tested simultaneously, no correction of Type I error was considered required for testing each hypothesis (i.e., a Type I error of 0.05 [2-sided] could be used to test each hypothesis).

The primary efficacy analysis was carried out on an intent-to-treat (ITT) basis, using the last-observation-carried-forward (LOCF) method for imputing data. The intent-to-treat population was defined as consisting of all randomized patients who received at least one dose of study medication and had at least a pre- and post-baseline assessment for one of the primary efficacy variables. The primary analysis of cognitive function was based on the change from baseline score for the ADAS-Cog; the treatment groups were compared using least square means derived from an analysis of covariance model with the following explanatory variables: treatment, country, and the baseline total ADAS-Cog score. The primary analysis for the ADCS-CGIC was to be a treatment comparison using a Cochran-Mantel-Haenszel test with modified ridit scores with country as stratification variable.

6.2.2 Efficacy Results

1195 patients were randomized of whom 1190 patients received study drug. The number of patients randomized to, and completing the study in each treatment group is summarized in the following table

Category	Treatment Group			
	Exelon® 20 cm^2 N (%)	Exelon® 10 cm^2 N (%)	Exelon® Capsule N (%)	Placebo N (%)
Randomized	303 (100.0)	293 (100.0)	297 (100.0)	302 (100.0)
Completing Study	241 (79.5)	229 (78.2)	234 (78.8)	266 (88.1)

The mean change from baseline to Week 24 in the ADAS-Cog was -1.6, -0.6, and 1.0 in the Exelon® 20 cm^2, Exelon® 10 cm^2, and placebo groups, respectively.

The mean ADCS-CGIC score at Week 24 was 4.0, 3.9, and 4.2, in the Exelon® 20 cm^2, Exelon® 10 cm^2, and placebo groups, respectively.

At Step 1 of the FDA-required primary efficacy analysis (the comparison of the 20 cm^2 Exelon® patch with placebo), the p-values were < 0.001 and 0.054 for the ADAS-Cog change from baseline score at Week 24 and the ADCS-CGIC rating at Week 24, respectively. These results were considered to provide substantial evidence of the superiority of the 20 cm^2 patch over placebo and sufficient for the sponsor to proceed to Step 2.

At Step 2 of the FDA-required primary efficacy analysis (the comparison of the 10 cm^2 Exelon® patch with placebo), the p-values were 0.005 and 0.010 for the ADAS-Cog change from baseline score at Week 24 and the ADCS-CGIC rating at Week 24, respectively. These results were considered to demonstrate the superiority of the 10 cm^2 patch over placebo.

The results of several sensitivity analyses were judged to be consistent with those of the primary efficacy analysis above for the ADAS-Cog change from baseline score, and, as already mentioned, for the ADCS-CGIC, both at Week 24.

No treatment differences that were even nominally statistically significant were seen when the 20 cm^2 and 10 cm^2 Exelon® patches were compared with placebo on the change from baseline to Week 24 in the Neuropsychiatry Inventory and Ten-Point Clock Test scores; nominally statistically significant differences were however seen on the Mini-Mental Status Examination and Trailmaking Test A change scores.

6.2.3 Safety Results

Safety assessments in this trial including the following: adverse events, vital signs, electrocardiograms, and formal assessments of skin irritation at the site of patch application.

In Study 2320, the qualitative spectrum of adverse events in patients administered the transdermal formulation of Exelon® was no different from that seen with the capsule formulation (with the exception of application site reactions). The incidence of specific, common, mainly gastrointestinal, adverse events was higher in those assigned to the 20 cm^2 patch than in those assigned to the 10 cm^2 patch (for example, the incidence of nausea and vomiting were about 21% and 19%, respectively, in those assigned to the 20 cm^2 patch, as compared with 7% and 6%, respectively, in those assigned to the 10 cm^2 patch); at the same time, the incidence of such adverse events seen in patients receiving the 20 cm^2 patch was similar to that seen in those receiving the capsule formulation in a dose of 6 mg BID. The transdermal formulation of Exelon® was tolerated well at the site of skin application and its adhesiveness was satisfactory.

7 Biometrics Review Of Application

The primary Biometrics review of the current application was completed by Julia Luan, PhD, on July 25, 2012.

She has independently replicated the sponsor's analysis of the primary efficacy measures.

She concludes that since a statistically significant difference between the treatment groups was not seen on the change from baseline to Week 48 in the ADAS-Cog total score, one of the study's two co-primary efficacy parameters, and since a "win" on both co-primary efficacy parameters is required for demonstrating efficacy in mild to moderate Alzheimer's Disease, there is insufficient statistical evidence to support the efficacy of the 15 cm^2 Exelon® Patch relative to the 10 cm^2 Exelon® Patch.

Please see Dr Luan's review for further details.

8 Other Agency Reviews

Agency reviews have also been provided by the following:

- The Division of Consumer Drug Promotion of the Office of Prescription Drug Promotion (Meeta Patel, PharmD)
- The Division of Professional Drug Promotion of the Office of Prescription Drug Promotion (Quynh-Van Tran, PharmD)
- The Division of Medical Policy Programs of the Office of Medical Policy Initiatives (Twanda Scales, RN, MSN/Ed)
- The Study Endpoints and Labeling Development Team (Eric Brodsky, MD)
- The Division of Medication Error Prevention and Analysis (Jung Lee, RPh)
- The Division of Risk Management (Reema Mehta, PharmD, MPH).

While the views expressed in those consultations are not described further here, they have been taken into full consideration by the Division in finalizing product labeling. Please refer to each review for further details.

9 Advisory Committee Meeting

No Advisory Committee meeting has been held or is planned to discuss this application.

10 Pediatrics

As is widely known, Alzheimer's Disease is a medical condition occurring exclusively in adults. There is no reason to believe that the Exelon® Patch in any strength has or will be widely used in children. Thus, a Pediatrics section is inapplicable to this application.

11 Other Relevant Regulatory Issues

11.1 Study Audit By Office of Scientific Investigations

2 clinical study sites participating in Study D2340 were audited by the Office of Scientific Investigations with the results described in a Clinical Inspection Summary completed by Antoine El-Hage, PhD, on July 19, 2012.

Both sites were located in Germany.

The Clinical Inspection Summary describes the results of the audit as being broadly reliable and acceptable.

11.2 Financial Disclosures

The sponsor has provided financial information for clinical investigators participating in Study D2340 entirely in accord with Agency recommendations. The information provided does not suggest that the financial arrangements described would influence the integrity of the data for Study D2340 contained in this submission.

12 Recommendations In Primary Medical Review Of Application

As already noted, the primary clinical review of this application was performed by Nicholas Kozauer, MD, whose review may be referred to for full details.

Dr Kozauer has recommended that the 15 cm^2 Exelon® Patch (which has a nominal release rate of 13.3 mg of rivastigmine every 24 hours) be approved for the treatment of both mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's Disease.

Dr Kozauer has presented a detailed argument in support of his recommendation. Among the elements that he has cited in support of his recommendation are the following.

- There is an adequate regulatory precedent for a single efficacy trial to serve as the basis for approving a higher dose of an already-marketed medication, as is the case with the current application.

- The Exelon® Patch was originally approved for the treatment of mild to moderate dementia associated with Parkinson's Disease based on the results of Study D2320 which was conducted only in patients with mild to moderate Alzheimer's Disease; the assumption made by the Agency at that time was that since the efficacy of the oral formulations of Exelon® had been demonstrated in mild to moderate dementia associated with Parkinson's Disease, the efficacy of the Exelon® Patch for the same indication could be assumed provided that the efficacy of the Exelon® Patch could be

demonstrated in mild to moderate Alzheimer's Disease. The same consideration applies to the current application as well

- The Agency has required that the efficacy of a product in mild to moderate Alzheimer's Disease should be demonstrated on cognitive and global (or functional) co-primary efficacy measures, a requirement that was incorporated into the design of Study D2340. In that study, the primary efficacy analysis of the ADAS-Cog (i.e., change from baseline to Week 48 of the double-blind phase) score did not indicate a statistically significant superiority of the 15 cm^2 Exelon® Patch over the 10 cm^2 Exelon® Patch; however, there was a (nominally) statistically significant superiority of the 15 cm^2 Exelon® Patch over the 10 cm^2 Exelon® Patch on the change in ADAS-Cog score from baseline to Week 24 of the double-blind phase together with a statistically significant (either actual or nominal) superiority of the 15 cm^2 patch over the 10 cm^2 patch on the instrumental ADCS-ADL at all timepoints, both indicating that the 15 cm^2 Exelon® Patch provided an overall clinical benefit at least through Week 24.

- There have been regulatory precedents where either a higher dose strength or a new formulation of an already-marketed acetylcholinesterase inhibitor has been approved for the treatment of Alzheimer's Disease despite demonstrating an effect on only one of two co-primary efficacy parameters. Particularly relevant to the current application was the approval of the 23 mg tablet formulation of Aricept® (donepezil hydrochloride) despite an effect being seen only on the Severe Impairment Battery (the cognitive co-primary instrument), but not on the Clinician Interview-Based Impression of Change-Plus (the global co-primary efficacy measure) in a 24-week clinical trial conducted in patients with moderate to severe Alzheimer's Disease in which the 23 mg tablet was compared with the 10 mg tablet of Aricept®

- In the past, treatments for Alzheimer's Disease have all been approved based on clinical trials that were only 12-24 weeks in duration. In Study D2340, the relatively high proportion of dropouts at Week 48 may have contributed to the difficulty demonstrating a treatment benefit on the ADAS-Cog at the 15 cm^2 patch dose relative to the 10 cm^2

- While gastrointestinal adverse events (except for diarrhea) were more frequent in the 15 cm^2 patch treatment group than in the 10 cm^2 treatment group in Study D2340, the majority of those events were mild to moderate in severity and resolved with longer durations of treatment, and there was no difference in the incidence of discontinuations between the two treatment groups on account of gastrointestinal events other than vomiting (5 patients in the 15 cm^2 discontinued on account of vomiting compared with 1 patient in the 10 cm^2 group). Although there were significant differences in design between the 2 studies, the safety findings at the 15 cm^2 patch dose in Study D2340 were comparable with those at the same dose in Study D2320.

13 Labeling

The Prescribing Information that originally accompanied this application covered both the currently-approved (i.e., 5 cm^2 and 10 cm^2) and proposed (i.e., 15 cm^2) strengths of Exelon® Patch, but has been further modified by the sponsor during this review period in response to a request from the Agency, as explained below.

When the current application (efficacy supplement) was first submitted, internal Agency deliberations directed at modifying the existing label for the Exelon® Patch (5 cm^2 and 10 cm^2) were already ongoing. After those deliberations were completed, the sponsor was provided with an edited version of that label in a letter from the Agency dated December 28, 2011, and asked in that letter to modify the Prescribing Information originally submitted with the current application accordingly. On February 14, 2012, the sponsor responded to the Agency letter of December 28, 2011 with an updated version of the Prescribing Information incorporating a number of the changes recommended by the Agency, but also proposing alternative text.

The Prescribing Information submitted by the sponsor on February 14, 2012 has been further reviewed by staff across the pertinent spectrum of review disciplines and finalized both within the Agency, and with the sponsor at the time of completion of this review. In my opinion, the label is acceptable and adequately addresses the concerns regarding both the efficacy and safety of this formulation that I have outlined in the next section.

The actual contents of the Prescribing Information are not further described here.

14 Recommendations/Risk-Benefit Assessment

I recommend that the 15 cm^2 Exelon® Patch (rivastigmine transdermal system) be approved for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's Disease, under the conditions of use described in product labeling approved by the Agency.

The above recommendation is based on a risk-benefit assessment that is only slightly disposed in favor of the proposed new product. That assessment is summarized further below.

Significant components of that risk-benefit assessment that could be considered unfavorable to the approval of the 15 cm^2 Exelon® Patch are the following:

- The lack of evidence for efficacy for that dose strength on one of the co-primary efficacy parameters, the change from baseline to Week 48 in ADAS-Cog total score, a standard efficacy measure used in clinical trials in mild to moderate Alzheimer's Disease and one that measures a core component of Alzheimer's Disease, namely cognition. As already noted, this deficiency has led Dr Julia Luan, the primary Biometrics reviewer of this application to recommend against the approval of the 15 cm^2 Exelon® Patch.

- A higher incidence of gastrointestinal adverse events, including nausea and vomiting, in those administered the 15 cm^2 Exelon® Patch, when compared with those who received the 10 cm^2 Patch.

However:

- A nominally statistically significant superiority of the 15 cm^2 patch over the 10 cm^2 patch was seen on the change from baseline to Week 24 in the ADAS-Cog (albeit with an even smaller effect size than is commonly seen in clinical trials conducted with acetylcholinesterase inhibitors in mild to moderate Alzheimer's Disease). The Agency has required that clinical efficacy trials in mild to moderate Alzheimer's Disease be at least 12 to 24 weeks in duration, with the majority of clinical trials of acetylcholinesterase inhibitors upon which their approval being 24 weeks long, and with none being of longer duration. There is no reason why the same standard should not apply to the results of Study 2340, even if the benefits of the 15 cm^2 patch over the already-approved 10 cm^2 were judged to be demonstrably short-lived.

- The efficacy of the 15 cm^2 patch relative to the 10 cm^2 patch did meet the Agency's usual standard for clinical meaningfulness in this setting.

- While vomiting is the gastrointestinal event that is arguably of greatest concern in elderly subjects, the proportion of patients with vomiting among those administered the 15 cm^2 patch was less than twice the proportion of patients with vomiting in the group administered the already-approved 10 cm^2 patch, with the number of patients discontinuing the study drug in either treatment group on account of that adverse event being very small.

Given the very small number of drugs that have been approved for the treatment of Alzheimer's Disease and the limited nature of their benefits, a new product that may offer an advantage over available treatment, even if only on a temporary basis, is worthy of approval provided the risks of the new product do not outweigh its advantages. It would appear that those requirements have been fulfilled for the 15 cm^2 Exelon® Patch, however modest the efficacy of that transdermal formulation.

I concur with Dr Kozauer that the efficacy of the 15 cm^2 Exelon® Patch does not need to be separately demonstrated in patients with dementia associated with Parkinson's Disease for that patch strength to be approved for the same indication; the basis for that view is the same as that first used to approve the Exelon® Patch – in lower strengths - for that indication.

Ranjit B. Mani, MD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RANJIT B MANI
08/31/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22083 (S-016)
Priority or Standard	Standard
Submit Date(s)	10/31/2011
Received Date(s)	10/31/2011
PDUFA Goal Date	8/31/2012
Division / Office	Division of Neurology Products/OND/ODEI
Reviewer Name(s)	Nicholas A. Kozauer, MD
Review Completion Date	7/17/2012
Established Name	Rivastigmine Transdermal Patch
(Proposed) Trade Name	Exelon® Patch
Therapeutic Class	Acetylcholinesterase Inhibitor
Applicant	Novartis Pharmaceutical Corporation
Formulation(s)	Transdermal Patch
Dosing Regimen	15cm^2 patch (13.3 mg rivastigmine/24 hours) administered once daily
Indication(s)	Alzheimer's Disease Parkinson's Disease Dementia
Intended Population(s)	Mild to Moderate Alzheimer's Disease; Mild to Moderate Parkinson's Disease Dementia

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend that the 15cm^2 Exelon® Patch (delivering 13.3mg rivastigmine/24 hours) be approved for the treatment of mild to moderate dementia of the Alzheimer's type and the treatment of mild to moderate dementia associated with Parkinson's disease.

1.2 Risk Benefit Assessment

This submission relies heavily on the results of a single clinical trial **[Study ENA713D2340 ("D2340")]** to support the approval of the 15cm^2 Exelon® Patch for the treatment of mild to moderate dementia of the Alzheimer's type and the treatment of mild to moderate dementia associated with Parkinson's disease (PDD). The overall objective of the trial was to demonstrate that patients with mild to moderate Alzheimer's disease (AD) who were found to decline clinically despite treatment with the currently marketed 10cm^2 Exelon® Patch could receive additional benefit from an increase to the 15cm^2 dose.

Study D2340 consisted of a 48-week initial open-label (IOL) phase where subjects were treated with the 10cm^2 Exelon® Patch (including a 4-week titration period on the 5cm^2 patch). Subjects who were found to decline clinically [Mini-Mental State Examination (MMSE) decrease of ≥2 from the previous visit OR ≥3 points from IOL baseline (Day 1)] between Weeks 24-48 of the IOL period were then randomized to either continue on the 10cm^2 patch or increase to the 15cm^2 patch in a subsequent 48-week double-blind (DB) treatment period. Subjects who did not decline clinically at the end of the IOL phase were continued on the 10cm^2 patch in an extended open-label (EOL) period. The trial's pre-specified co-primary efficacy endpoints were the differences between treatment groups in the change from DB baseline to DB Week 48 in the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) and the Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living (ADCS-IADL) scales. 1584 subjects were enrolled in the IOL phase with 567 randomized in the DB phase in an equal ratio to both treatment arms (283 and 280 in the 10 and 15cm^2 arms, respectively).

In this case, there is ample regulatory precedent with respect to the use of a single clinical trial to support the use of a higher dose of an already marketed medication. Specifically, Section 505(d) of the FD&C act explicitly states that "if the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence."

The submission also references selected safety data from **Study ENA713D2320 ("D2320")** which served as the pivotal trial in the original approval of the 5 and 10cm^2 Exelon® Patch doses on July 6, 2007. This was a 24-week double-blind, placebo-controlled, parallel-group trial that compared 10cm^2 and 20cm^2 doses of the Exelon® Patch, 12mg/day of the Exelon®

capsule, and placebo. The 15cm^2 patch was used only as a 4-week titration step in that trial. The current submission presents safety data for the 15cm^2 dose in Study D2320 in comparison to the findings from Study D2340. Because of the significant differences in design, data from these trials was not pooled in the present analysis.

It should be noted that Study D2320 also served as the basis for the approval of the Exelon® Patch for the treatment of patients with mild to moderate PDD despite the enrollment of only AD subjects. The rationale behind this decision was that the demonstrated efficacy of the Exelon® oral formulations in the PDD population could also be assumed for the Exelon® Patch, provided that efficacy could be demonstrated in AD subjects as was the case in Study D2320. The same logic was also applied to the clinical evaluation of the current submission.

Historically, effect sizes observed in the clinical trials for all of the currently approved treatment for AD have been relatively small. As a result, the Division continues to enforce the longstanding policy that trials for AD treatments incorporate the use of co-primary efficacy endpoints. One endpoint must be a measure of cognition (core to the disease process) while the other is either a global clinical rating or a functional assessment. The principle behind this approach is the belief that a benefit on the latter will speak to the clinical meaningfulness of any observed differences on the former. In utilizing the ADAS-cog and ADCS-IADL scales, Study D2340 contained the required elements of trial design in this regard. The change from DB baseline scores between treatment groups [in the intent-to-treat (ITT) last observation carried forward (LOCF) population] statistically separated on the ADCS-IADL at Week 48, which was the timepoint selected for the pre-specified primary efficacy analysis [+2.2 (0.8, 3.6) p=0.002]. Unfortunately, no statistically significant difference in the change from DB baseline at DB Week 48 was observed on the ADAS-cog [-0.8 (-2.1, 0.5) p=0.227]. As such, Study D2340 failed to meet its pre-specified efficacy outcome criteria. However, for reasons further outlined below, I believe that the results from Study D2340 nevertheless support the approval of the 15cm^2 Exelon® Patch.

The design of Study D2340 is somewhat analogous to a dose-ranging study albeit without the presence of a placebo group. When viewed in that context, the lack of a statistical separation on ADAS-cog scores at Week 48 alone would not necessarily prohibit the approval of the 15cm^2 patch. The challenge in that interpretation, however, lies in the fact that subjects at DB Week 48 would have already been dosed with the 10cm^2 Exelon® Patch for between 72-96 weeks (including the IOL phase). There is no well-controlled clinical trial data to support (or refute) the contention that the 10cm^2 patch itself would separate from placebo after such a prolonged duration of treatment. The usefulness of the dose-ranging analogy becomes more relevant though in relation to the fact that the treatment arms did statistically separate from each other on ADAS-cog scores at DB Week 24 [-1.3 (-2.5, -0.2) p=0.027]. At this point subjects would have been dosed with the Exelon® Patch (inclusive of the 10 and 15cm^2 doses) for between 48-72 weeks. While there is still no evidentiary basis for an argument of the superiority of the 10cm^2 patch relative to placebo after this duration (i.e., at DB Week 24), the fact that the treatment arms statistically separated from each other on the change in ADAS-cog scores remains significant. Specifically, this finding strongly suggests that the 15cm^2 patch conveys some additional cognitive benefit over the 10cm^2 at that point, irrespective of the reality that degree of benefit over placebo cannot be defined. When viewed in tandem with the statistically significant differences between the treatment groups on the ADCS-IADL scale at all timepoints, it becomes

clear that the 15cm^2 patch offers an overall clinical benefit to patients at least through DB Week 24 of the trial.

One can also look to several examples of regulatory precedent in AD drug approvals that further support the preceding interpretation of Study D2340. Trials supporting the approval of two of the currently marketed treatments for AD [Aricept™ 10mg (donepezil HCL) and Razadyne® ER 24 mg (galantamine HBr)] also demonstrated a lack of separation between these doses and the next highest doses (despite beating placebo) on one of the two co-primary efficacy endpoints. In both instances, however, the higher dose was still approved with the view that some patients could reasonably still be expected to benefit from it. An even more relevant recent example is the approval of the 23mg dose of Aricept™ in 2010. In brief, the approval of this dose for the treatment of moderate to severe AD was based on the results of a single 24-week trial comparing the 23mg dose to the 10mg dose as an active comparator (there was no placebo group). At 24 weeks the treatment arms statistically separated on the cognitive outcome measure [the Severe Impairment Battery (SIB)] but not on the global rating scale [the Clinician's Global Impression of Change-Plus Caregiver Input scale (CIBIC+)]. The 23mg dose was still approved based on similar logic as described above. Mainly, that there was no reason to believe that the 23mg dose would not be as effective as the 10mg dose which has proven efficacy after that duration of use. It is worth restating that there is not a similar basis for a presumed benefit of the 10cm^2 patch over placebo on the ADAS-cog in the DB phase of Study D2340 in that subjects would have already been dosed with the Exelon® Patch in the IOL phase (and by definition were decliners). That said, the fact remains that the 15cm^2 did separate from the 10cm^2 arm at DB Week 24 on the ADAS-cog unlike the Aricept 23mg example where no separation was seen at all on the CIBIC+. Therefore, while inference of a benefit over placebo at Week 24 was essential in the case of Aricept 23mg, this assumption becomes less relevant in the current situation.

There is little question that the applicant's decision to incorporate a 48 week DB treatment period into the design of Study D2340 has introduced the greatest challenge into the interpretation of the trial's findings. Historically, treatments for AD have been approved based on trials lasting 12-24 weeks. As these approved agents are widely accepted to confer a solely symptomatic benefit, a 24-week time period is more that adequate to observe a difference between treatment arms. The rationale behind the choice of the 48-week duration is largely unclear from the submission. The relatively high percentage of drop-outs, which is not at all unexpected in this frail population, between DB Weeks 24-48 (29 and 45 in the 15cm^2 and 10cm^2 arms, respectively) may undoubtedly have contributed to the inability to detect a statistically significant difference in ADAS-cog scores at DB Week 48.

As mentioned above, the safety data provided in this submission is primarily derived from Study D2340 with some limited additional comparative data provided from Study D2320 where the 15cm^2 Exelon® Patch was used as a 4-week titration step. The adverse events (AEs) observed with the 15cm^2 patch were those expected for this class of medication and Exelon® in particular. Specifically, gastrointestinal AEs such as nausea and vomiting were the most commonly observed AEs that could be attributed to treatment. These AEs occurred at a generally higher rate in the 15cm^2 patch group relative to the 10cm^2 patch group as outlined in the following table (the incidence of diarrhea was roughly 8% in both groups):

Adverse Event (Preferred Term)	Exelon 10 cm2 N=283 N	%	Exelon 15 cm2 N=280 N	%
Decreased appetite	12	4.2	22	7.9
Nausea	19	6.7	42	15.0
Vomiting	22	7.8	36	12.9
Weight decreased	18	6.4	25	8.9

The majority of these AEs were mild to moderate in severity and tended to resolve with longer durations of treatment. The were no differences in the rates of discontinuations due to these AEs with the exception that 5 subjects in the 15cm^2 arm discontinued due to nausea as opposed to only 1 subject in the 10cm^2 arm. Overall, subjects in the 10cm^2 arm had a higher rate of discontinuation due to AEs (12.7 versus 9.6%, respectively). There was no difference in the occurrence of serious adverse events (SAEs) between the groups.

The limited safety data presented from Study D2320 demonstrated comparable safety findings to Study D2340 with respect to the 15cm^2 Exelon® Patch. Additionally, the occurrence of AEs of interest (e.g., gastrointestinal AEs) in Study D2320 was largely dose-proportional with incidences at the 20cm^2 dose approximately twice that of the 15 cm^2 group. Furthermore, gastrointestinal AEs with the 15cm^2 patch occurred at less then half the frequency relative to what was seen in the clinical trials supporting the currently marketed oral formulations of Exelon®. For example, the rates of nausea and vomiting were as high as 47 and 31%, respectively, in Alzheimer's disease patients in the oral formulation trials.

Ultimately, for the reasons described above, it is my opinion that the 15cm^2 Exelon® Patch provides an additional overall clinical benefit to patients with mild to moderate AD who decline despite treatment with the 10cm^2 patch. This benefit can also be assumed for patients with mild to moderate PDD as well. The results of Study D2340 suggest that this benefit persists through at least 24 weeks of treatment and also conveys some additional perceived functional benefit through at 48 weeks. While Study D2340 failed to meet its overall pre-specified efficacy objective due to the lack of a statistically significant difference between treatment arms in the change from DB baseline ADAS-cog scores at DB Week 48, this could be attributed in large part to the sequelae of an unreasonably long DB treatment period. As the overall safety profile of the 15cm^2 patch is otherwise acceptable, the prospect of offering patients the opportunity to benefit from a higher dose patch when the 10cm^2 dose is deemed no longer clinically beneficial supports the approval of the current application even if the degree of that benefit is more difficult to quantify beyond 24 weeks.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no clinical recommendations for any postmarket Risk Evaluation and Mitigation Strategies (REMS) at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no clinical recommendations for any postmarket requirements and/or commitments at this time.

2 Introduction and Regulatory Background

2.1 Product Information

The Exelon® Patch (rivastigmine transdermal system) is a once-daily, transdermal formulation of rivastigmine free base. Each patch is a thin, matrix-type transdermal system consisting of 3 layers.

Exelon® (rivastigmine) is a slowly reversible, brain selective, dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) of the carbamate type.

The current submission is intended to support to approval of the 15cm^2 Exelon® Patch (which contains rivastigmine tartrate at a release rate of 13.3mg/24 hours) for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease (PDD).

The following graphic, copied from the submission, further illustrates the construction of the 15cm^2 Exelon® Patch:

2.2 Table of Currently Available Treatments for Proposed Indications

The following table summarizes the other currently available treatments for AD:

Drug Name	Formulation	NDA	Initial Approval Date	Mechanism of Action	Indication
Cognex *(Tacrine)*	Capsule	20070	9/1993	Cholinesterase inhibitor	Mild-moderate AD
Aricept *(donepezil)*	Tablet (IR)	20690	11/1996	Acetylcholinesterase inhibitor	Mild-moderate AD (5 and 10 mg dose), Severe AD (10 mg dose)
	Oral Disintegrating Tablet (ODT)	21720	10/2004		
	23 mg tablet	22568	7/2010		Moderate-severe AD (23 mg)
Razadyne *(galantamine)*	Tablet (IR)	21169	6/2001	Cholinesterase inhibitor	Mild-moderate AD
	Solution	21224	2/2001		
	Extended release (ER)	21615	12/2004		
Exelon *(rivastigmine)*	Capsules	20823	4/2000	Cholinesterase inhibitor	Mild-moderate AD; mild-moderate PDD (since 2006)
	Oral solution	21025	4/2000		
	Transdermal Patch	22083	7/2007		
Namenda *(memantine)*	Tablet (IR)	21487	10/2003	NMDA antagonist	Moderate-severe AD
	Solution	21627	2/2005		
	Extended release (XR) capsule	22525	6/2010		

2.3 Availability of Proposed Active Ingredient in the United States

Exelon® (rivastigmine tartrate) was initially approved by the Agency on March 21, 2000 as immediate-release capsule and oral solution formulations for the treatment of mild to moderate dementia of the Alzheimer's type. Please refer to the primary reviews of NDA 20823 (for the immediate-release capsule formulation) and NDA 21025 (for the oral solution formulation), and to the current product labeling for both formulations, for full details of those applications.

The immediate-release capsule and oral solution formulations of Exelon® were also approved by the Agency for the treatment of mild to moderate dementia associated with Parkinson's Disease [under NDA 20823 (SE1-016) and NDA 21025 (SE1-008), respectively] on June 27, 2006.

The 10cm^2 Exelon® Patch (containing 9.5mg rivastigime/24 hours) was subsequently approved by the Agency on July 6, 2007 for the treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease (PDD). The 5cm^2 Exelon® Patch (containing 4.6mg rivastigime/24 hours) was also approved at that time as a titration dose to be used for 4 weeks prior to increasing to the target 10cm^2 patch. (b) (4)

(b) (4)

2.4 Important Safety Issues with Consideration to Related Drugs

The principal safety issues related to the use of acetylcholinesterase inhibitors in general, and to rivastigmine in particular, for the treatment of AD/PDD relate primarily to the potential for gastrointestinal adverse events (nausea, vomiting, diarrhea, and bleeding). Other less frequent but potential areas of concern include vagotonic effects on heart rate, bladder outflow obstruction, generalized convulsions, and the exacerbation of asthma or obstructive pulmonary disease.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Exelon® Patch has been developed under IND 54051 which was originally submitted to the Agency on September 10, 1997. The following are the major milestone meetings that have been held under that IND in relation to the current application:

- End-of-Phase 2 meeting (November 24, 2008)
- Pre-sNDA meeting (August 8, 2011)

The following are among the key agreements reached at the November 24, 2008 End-of-Phase 2 meeting:

- Study D2340 should include a co-primary global or functional measure in addition to the ADAS-cog which was proposed as the sole primary outcome measure at that time
- The primary efficacy analysis for Study D2340 should be conducted in the intent-to-treat population (defined as those subjects having at least one post-baseline assessment for both co-primary efficacy measures) using the last-observation-carried-forward method of imputation
- A single study, such as Study D2340, could support the approval of the 15cm^2 Exelon® Patch provided that the ADCS-ADL was used as a co-primary outcome measure and that the results of the trial were positive for evidence of efficacy

The following are among the key agreements reached at the August 8, 2011 Pre-sNDA meeting:

- The lack of a statistically significant difference on the ADAS-cog at Week 48 in Study D2340, which was one of the trial's pre-specified co-primary efficacy endpoints, would not be grounds for a refuse-to-file decision

- The sponsor should address any potential similarities/differences between the sponsor's planned application and the Agency's July 28, 2010 approval of the 23mg dose of Aricept® tablets for the treatment of moderate to severe AD. In particular, the pivotal trial included in that application failed to demonstrate a statistically significant benefit of the 23mg dose over an active comparator (Aricept® 10mg tablets) on the Clinician Interview-Based Impression of Change-Plus which was one of the study's co-primary endpoints.

2.6 Other Relevant Background Information

There is no other relevant background information to include in this review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A Clinical Inspection Summary (CSI) has been completed by Antoine El-Hage, PhD, of the Office of Scientific Investigations. Please see that document for full details.

The study sites inspected are summarized in the following table:

Name of CI and Site # (if known)	Number of Subjects Enrolled	Country	City	Protocol	Inspection Date	EIR Received	Final Classification
Jurgen Deckert, MD (318)	8	Germany	Wurzberg	ENA713D2340	March 19-22, 2012	Yes	VAI
Hermann-Josef Gertz, MD (307)	33	Germany	Leipzig	ENA713D2340	March 13-16, 2012	Yes	VAI

VAI= Voluntary Action Indicated

The CSI for these sites indicates that the data obtained from both sites were, in general, considered reliable and acceptable in support of the current application. Dr. Deckert's site was noted to have two subjects (0002 and 0006) who received mirtazipine during the trial. Although this is a permitted medication at stable doses, it appears that the use of mirtazipine in these subjects was not stable during the course of the trial. The CSI therefore suggests that consideration by the review division be given to excluding these subjects from the final analysis. However, as these deviations were unlikely to significantly impact the current clinical analysis, these subjects were not excluded from this review.

3.2 Compliance with Good Clinical Practices

Based on my review, it appears that the studies contained in this submission were conducted in accordance with acceptable standards with respect to informed consent, protocol violations, site specific issues, or any ethical infractions.

3.3 Financial Disclosures

The sponsor has adequately disclosed the relevant financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* These arrangements do not appear to raise questions about the integrity of the data submitted with this application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Based on a preliminary discussion, the CMC reviewers for this submission indicated that they did not anticipate any outstanding issues from their perspective that would preclude the approval of the 15cm^2 patch dose.

4.2 Preclinical Pharmacology/Toxicology

No new preclinical data has been provided in the current submission. Based on a preliminary discussion, the Pharmacology-Toxicology reviewers for this submission indicated that they did not anticipate any outstanding issues from their perspective that would preclude the approval of the 15cm^2 patch dose.

4.3 Clinical Pharmacology

Based on a preliminary discussion, the Clinical Pharmacology reviewers for this submission indicated that they did not anticipate any outstanding issues from their perspective that would preclude the approval of the 15cm^2 patch dose.

4.3.1 Mechanism of Action

Exelon® (rivastigmine) is a slowly reversible (pseudo-irreversible), brain selective, dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) of the carbamate type. Exelon® is thought to exert its therapeutic effect by enhancing cholinergic function (the loss of which is thought to be related to decreased cognitive performance). This is accomplished by increasing the concentration of acetylcholine through reversible cholinesterase inhibition.

4.3.2 Pharmacodynamics

No new pharmacodynamic information for the 15cm^2 Exelon® Patch has been provided in the current submission.

4.3.3 Pharmacokinetics

No new pharmacokinetic information has been provided in the current submission beyond what was reviewed in the original application for the approval of the Exelon® Patch.

The pharmacokinetic properties of the 15cm^2 Exelon® Patch were characterized in Study D2331 in Alzheimer's disease patients. Briefly, Study D2331 was an 8-week, open-label, parallel-group, ascending (titration) dose proportionality study evaluating the Exelon® 5cm^2, 10cm^2, and 20cm^2 transdermal patches and 1.5, 3, 4.5, and 6mg twice daily capsules at steady state in patients with mild to moderate AD. The primary objectives of Study D2331 were as follows:

- To explore the dose-pharmacokinetic exposure relationship of rivastigmine and its metabolite NAP226-90 following multiple applications of 5 cm^2, 10 cm^2, 15 cm^2 and 20cm^2 (FMI) rivastigmine patches

- To explore the dose-pharmacokinetic exposure relationship of rivastigmine and its metabolite NAP226-90 following multiple oral twice daily administrations of 1.5 mg, 3 mg, 4.5mg and 6 mg Exelon capsules

- To compare the bioavailability of rivastigmine and its metabolite NAP226-90 following rivastigmine patch with capsule administrations in patients with mild-to-moderate AD

A total of 25 patients were randomized to receive Exelon® Patch treatment with 13 patch patients completing all 4 study periods.

The following table, copied from the submission, summarizes the key pharmacokinetic findings from Study D2331:

Table 3-1 Rivastigmine exposure parameters following rivastigmine multiple o.d. patch applications in patients with mild-to-moderate Alzheimer's disease – (Study D2331)

Rivastigmine	C_{max} (ng/mL)	t_{max} (h)	C_{avg} (ng/mL)	AUC_{24h} (ng·h/mL)	$t_{½}$ (h)	FI *
5 cm² (9 mg loaded dose, n = 22)						
Mean ± SD	2.71 ± 1.23	-	1.93 ± 0.718	46.3 ± 17.2	-	0.58 ± 0.40
CV%	45.2	-	37.2	43.2	-	69.2
Median	2.57	8.0	1.98	47.6	-	0.61
Range	1.19-5.39	0.0-12.08	0.718-1.98	20.0-81.4	-	0.00-1.17
Geo. mean	2.45	-	1.80	43.2	-	-
CV% Geo. mean	49.7	-	40.7	40.7	-	-
10 cm² (18 mg loaded dose, n = 22)						
Mean ± SD	7.88 ± 2.88	-	5.29 ± 1.73	127 ± 41.4	-	0.77 ± 0.32
CV%	36.6	-	32.6	32.6	-	42.2
Median	7.79	8.0	5.40	129	-	0.76
Range	2.76-12.9	3.0-16.0	2.43-8.25	41.4-198	-	0.15-1.26
Geo. mean	7.32	-	4.99	120	-	0.69
CV% Geo. mean	43.1	-	38.1	38.1	-	57.4
15 cm² (27 mg loaded dose, n = 19)						
Mean ± SD	14.1 ± 6.30	-	9.71 ± 3.47	233 ± 83.2	-	0.72 ± 0.36
CV%	44.6	-	35.7	35.7	-	50.5
Median	15.3	8.0	10.6	255	-	0.61
Range	4.32-25.7	3.0-16.0	3.89-14.4	93.3-345	-	0.08-1.30
Geo. mean	12.6	-	9.03	217	-	0.60
CV% Geo. mean	55.4	-	42.9	42.9	-	81.3
20 cm² (36 mg loaded dose, n = 13)						
Mean ± SD	19.5 ± 7.51	-	14.4 ± 5.28	345 ± 127	3.37 ± 0.73	0.57 ± 0.35
CV%	38.4	-	36.7	36.7	21.7	62.3
Median	20.7	8.0	15.4	370	3.08	0.63
Range	7.55-33.7	0.0-12.0	5.83-22.0	140-529	2.61-5.02	0.00-1.12
Geo. mean	18.1	-	13.3	320	3.30	-
CV% Geo. mean	44.8	-	45.3	45.2	20.2	-

- = not available or not applicable; * FI = fluctuation index

The following are the key conclusions that have been drawn from Study D2331 (which have been reviewed in detail in the original marketing application for the Exelon® Patch):

- The rivastigmine patch uses the free base of rivastigmine as it has a better flux rate and enables the loading of higher doses of rivastigmine into each patch; the oral formulations, on the other hand, use the hydrogen tartrate salt of rivastigmine.

- 5 different sizes (strengths) or rivastigmine patch have been evaluated in clinical trials. These are listed in the table below

Rivastigmine patch size	Rivastigmine content
5 cm^2	9 mg
7.5 cm^2	13.5 mg
10 cm^2	18 mg
15 cm^2	27 mg
20 cm^2	36 mg

- After the application of the rivastigmine patch, the T_{max} was at about 13 to 16 hours after single patch application and 8 hours at steady state

- The rivastigmine patch produced a lower C_{max} and higher AUC_{0-24} as compared with the 2 approved oral formulations of rivastigmine (at matching doses). For example, under steady-state concentrations, the largest size patch (20 cm^2) produced a 1.5-fold lower C_{max} and a 1.8-fold higher AUC_{0-24} as compared with the highest dose of the Exelon® capsule (12 mg/day). The patch also showed less peak-trough fluctuations in plasma concentrations of rivastigmine than the oral formulation

- Over a 24-hour period, about 50% of the drug load in each patch (regardless of size/strength) was released from the system, as assessed by drug residual in each patch, and as shown in the following table

Rivastigmine patch size	Rivastigmine content	Estimated rivastigmine release rates over 24 hours
5 cm^2	9 mg	4.6 mg
10 cm^2	18 mg	9.5
15 cm^2	27 mg	13.3
20 cm^2	36 mg	17.4

- After the application of a single patch, rivastigmine reached the systemic circulation with an absorption lag time of 0.6 to 1.5 hours after application of a single patch; the principal metabolite of rivastigmine, NAP226-90 was detected in the systemic circulation after a lag time of 1.2 to 2.3 hours. Population pharmacokinetic modeling estimated that the lag time at steady state after application of the rivastigmine patch was 42 minutes and 1.5 hours for rivastigmine and NAP226-90, respectively (the respective lag times for rivastigmine and NAP226-90 after oral administration were 0 and 11 minutes).

- The relative bioavailability of the 3 mg rivastigmine immediate-release coral solution and the 10 cm^2 rivastigmine patch were compared: the AUC_∞ of the patch was 5.2 times higher and the C_{max} 0.8 times lower than after the oral solution. After normalization for dose (mg of rivastigmine released from the patch (and body weight), the relatively bioavailability of the patch versus the oral solution (based on the patch/solution ratio) was 2.5 for AUC_∞ and 0.31 for C_{max}.

- The metabolite-to-parent AUC_∞ ratio was 0.7 after the patch versus 3.5 after oral administration, indicating that the metabolism of rivastigmine was less after transdermal administration than after oral administration.

- Exposure to rivastigmine, based on C_{max} and AUC_∞ increases over-proportionately with increasing dose. On dose escalation through the 5, 10, 15, and 20 cm^2 patch sizes, the increase in rivastigmine exposure to the lowest dose of 5 cm^2 dose was 2.5, 4.9, and 7.8-fold for the 10, 15, and 20 cm^2 patch sizes, respectively (the shift from linear increases in exposure was less with the patch formulation than with oral formulations)

- There was no correlation between the bioavailability of rivastigmine and degree of adhesiveness of the patch

- The intra-subject co-efficient of variation for C_{max} and AUC_{∞} ranged from 19-42% and 18-56%, respectively. The inter-subject coefficient of variation for C_{max} and AUC_{∞} ranged from 44-60% and 52-80%, respectively. The variability was considered moderate, and less than for the oral formulations.

- Elimination half-life ranged from 2.2 to 3.9 hours after patch application versus 1.4 hours after oral or intravenous administration.

- The highest exposure to rivastigmine was obtained when the patch was applied to the upper back, chest or upper arm and lowest when applied to the thigh or lower abdomen.

- After application of the rivastigmine patch, urinary excretion was mainly in the form of NAP266-90 and its sulfate conjugate

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The current submission provides data from the following single clinical trial in support of the efficacy of the 15cm^2 Exelon® Patch:

Study Number	Primary Objective/Population	Patients	Duration	Dose/Day	Primary Efficacy Endpoints
D2340	Efficacy, safety, and tolerability in patients with mild to moderate dementia of the Alzheimer's type	Open-label phase: 1584 Double-blind phase: 567 (randomized)	24-48 week initial open-label (IOL) 48 week double-blind (DB)	IOL phase: Open-label treatment with target dose of 10cm^2 DB phase: Once daily 10cm^2 or 15cm^2 patch	Change from DB baseline to Week 48 of the DB treatment phase in ADAS-cog total score and ADCS-Instrumental ADL total score

While Study D2340 was also the main source of safety data for the current application, the sponsor also refers to Study D2320 which served as the single pivotal trial in support of the currently marketed dosages of the Exelon® Patch. As Study D2320 only used the 15cm^2 dose as a titration step, the presentation of data from this trial has not been pooled and is provided in a comparative format only. A tabular summary of Study D2320 is as follows:

Study Number	Objective/Population	Patients	Duration	Dose/Day	Efficacy Endpoints
D2320	Efficacy, safety, and tolerability in patients with mild to moderate dementia of the Alzheimer's type	1040 patients (260 per group)	24 weeks	Placebo, Exelon® Patch 10cm^2 daily, Exelon® Patch 20cm^2 daily, Exelon® oral capsules 6mg twice daily	Change from baseline to Week 24 in ADAS-cog and ADCS-CGIC scores

5.2 Review Strategy

This application consisted of new data that were presented only for Study D2340 in support of the marketing registration of the 15cm^2 Exelon® Patch. The submission also references Study D2320 which served as the foundation for the approval of the 10cm^2 Exelon® Patch. Study D2320 only used the 15cm^2 patch as a 4-week titration step and therefore safety data from this trial were not pooled with that from Study D2340 due to fundamental differences in trial design. Rather, selected safety data from Study D2320 were presented in a comparative format to Study D2320.

The approach used in this review was to focus most directly on the analysis of Study D2340 as a single study in Section 5.3.1. The safety data from Study D2320 was then discussed separately in Section 5.3.2 and commentary as to the comparisons made with Study D2340 are included therein.

Sections 6 (Review of Efficacy) and 7 (Review of Safety) of the Clinical Review Template were largely omitted from this review given the heavy reliance on the results of a single trial (D2340) and the lack of any additional pooled data for either the efficacy or safety analyses. Instead, Sections 6 and 7 were used to summarize the key efficacy and safety conclusions, respectively, which were largely restricted to an interpretation of the results of Study D2340.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study ENA713D2340

5.3.1.1 Title

A 48-week, multicenter, randomized, double-blind, parallel group evaluation of the comparative efficacy, safety, and tolerability of Exelon® 10 and 15 cm^2 patch in patients with Alzheimer's disease showing cognitive decline during an initial open-label phase

5.3.1.2 Objectives

5.3.1.2.1 Primary

To compare the efficacy of target Exelon 10 cm^2 patch versus target Exelon 15 cm^2 patch in patients who have demonstrated cognitive decline in the initial open-label (IOL) phase (Exelon 10 cm^2 patch) with respect to:

- The change from DB randomization baseline to Week 48 of the DB phase in cognition as assessed by the ADAS-cog subscale, and
- The change from DB randomization baseline to Week 48 of the DB phase in instrumental activities of daily living as assessed by the ADCS-Instrumental ADL subscale

5.3.1.2.2 Secondary

To compare the efficacy of target Exelon 10 cm^2 patch versus target Exelon 15 cm^2 patch in patients who have demonstrated cognitive decline in the IOL phase (Exelon 10 cm^2 patch) with respect to:

- The time to functional decline (i.e., interval between DB randomization baseline to first decline from DB randomization baseline) in instrumental activities of daily living as assessed by the ADCS-Instrumental ADL subscale over the 48-Week DB phase;
- The change from DB randomization baseline to Week 48 of the DB phase in attention and executive function as assessed by the Trail Making Test (TMT) Parts A and B;
- The change from DB randomization baseline over the 48-Week DB phase in neuropsychiatric symptoms as assessed by the 10-item Neuropsychiatric Inventory (NPI-10)

To compare the safety and tolerability of target Exelon 10 cm^2 patch versus target Exelon 15 cm^2 patch in the DB phase with respect to:

- The incidence of adverse events (AEs), serious AEs (SAEs), and discontinuations due to adverse events (AEDs);
- Changes in vital signs [particularly blood pressure (BP), pulse, and body weight];
- The incidence of gastrointestinal (GI) AEs (particularly nausea and vomiting), the degree of burden (severity x incidence) of GI AEs (nausea and vomiting) and discontinuations due to GI AE;
- The incidence of treatment emerging cardiac abnormalities detected on 12-lead ECG (particularly the PR and RR intervals)

5.3.1.2.3 Exploratory

The submission outlines the following exploratory objectives which have been addressed in the study report contained in the submission:

<u>Open-label phase</u>

- Evaluate the proportion of patients with cognitive decline and the time to clinically significant decline as a function of baseline disease severity (and other sub-populations) in the OL phase;
- Assess the effect of Exelon patch treatment on the reduction of systemic inflammatory markers

<u>Double-blind phase</u>

- Explore if patient characteristics or changes in clinical parameters during the IOL phase on Exelon 10 cm^2 patch predict additional benefit on Exelon 15 cm^2 patch in the DB phase (e.g. improvement in cognition after initial 8 weeks of OL treatment with Exelon 10 cm^2 patch; more advanced AD, older age, or the presence of specific symptoms - such as hallucinations - at baseline of OL phase).

- Explore influence of biomarkers:

    - Whether elevated systemic inflammatory markers at baseline of OL phase predict additional benefit on target Exelon 15 cm^2 patch in the DB phase;

    - In patients with moderate AD, if butyrylcholinesterase (BuChE) wt/wt genotype predicts additional benefit on target 15cm^2 patch in the DB phase

5.3.1.3 Design

The trial was a prospective, multicenter, randomized, double-blind, double-dummy, parallel group design. Specifically, the trial was designed to compare the efficacy and safety of treatment with Exelon 15 cm^2 patch to Exelon 10 cm^2 patch during a 48 week DB treatment phase in patients who demonstrated functional and cognitive decline after 24 to 48 weeks of treatment with Exelon 10 cm^2 patch during a prior IOL treatment period.

The following graphic, copied from the submission, further illustrates the design of the trial:

Phase	Screening		Initial open-label						Double-blind treatment				
Visit	1	2	3	4	5	6	7	8	1.1	1.2	1.3	1.4	1.5
Week	< -5	Day 1	4	8	12	24	36	48	4	12	24	36	48*

	Titration	Maintenance	Additional	Maintenance for decliners
				Exelon 10 cm^2 patch
	Exelon 5 cm^2	Exelon 10 cm^2 patch with demonstrated decline at Week 24, 36 or 48		
				Exelon 15 cm^2 patch
Treatment: None				Extended open-label for (non-decliners)
				Visit: 3.1 / 3.2 / 3.3 / 3.4
				Week: 12 / 24 / 36 / 48
		Exelon 10 cm^2 patch without demonstrated decline at Week 48		Exelon 10 cm^2 patch

Baseline for the initial open-label (IOL) treatment phase was Day 1 prior to first dose. Baseline for the double-blind (DB) treatment phase was the DB randomization day.

Additional visits were allowed for patients without demonstrated functional and cognitive decline during IOL maintenance visits.

Patients randomized to the DB treatment phase began treatment with DB medication on the day following randomization. Down-titration was allowed as required to address tolerability problems.

* or premature discontinuation visit.

5.3.1.4 Duration

As indicated in the graphic in the preceding section of this review, the study was composed of the following phases (and durations):

- Screening phase (up to 5 weeks)

- IOL phase (24- to 48-weeks)
  Patients were initially treated with Exelon 5 cm^2 patches for 4 weeks, and subsequently titrated to Exelon 10 cm^2 patches. Patients were evaluated at Weeks 24, 36, and 48 of the IOL for functional decline (per investigator judgment) and cognitive decline [MMSE decrease of ≥2 from the previous visit OR ≥3 points from IOL baseline (Day 1)]

- DB phase (48 weeks)
  Patients who demonstrated decline during the IOL phase were randomized in equal proportions to 1 of 2 treatment arms (Exelon 10 cm^2 or Exelon 15 cm^2 patches).

- Extended open-label (EOL) phase (48 weeks)
  Patients who did not demonstrate decline after 48 weeks in the IOL phase were offered continued treatment with a maintenance dose of Exelon 10 cm^2.

5.3.1.5 Sample Size (Planned)

A total of 1571 patients were planned for enrollment in the IOL phase with a planned sample size in the DB phase consisting of 432 subjects per treatment arm (864 subjects total).

5.3.1.6 Subject Selection

5.3.1.6.1 Key Inclusion Criteria

- Diagnosis of AD according to the DSM-IV criteria for dementia of the Alzheimer's type
- Clinical diagnosis of probable AD according to the NINCDS/ADRDA criteria, with the required brain scan [magnetic resonance imaging (MRI) or computed tomography (CT)] performed within 2 years prior to the IOL baseline visit
- MMSE score of 10 to 24, inclusive
- Males and females not of child-bearing potential (surgically sterile or 1 year postmenopausal)

5.3.1.6.2 Key Exclusion Criteria

- Dementia or medical or neurological conditions other than AD that could interfere with the evaluation of patient response to study medication
- Current diagnoses of uncontrolled seizure disorder; severe or unstable cardiovascular disease; bradycardia (< 50 bpm); sick-sinus syndrome, or conduction defects; acute, severe, or unstable asthmatic conditions; uncontrolled peptic ulceration or gastro-intestinal bleeding within the last 3 months; clinically-significant urinary obstruction
- Allergy to topical products containing vitamin E; known exaggerated pharmacological sensitivity or hypersensitivity to drugs similar to rivastigmine or to other cholinergic compounds; or active skin lesion/disorder that would prevent the patient from using a transdermal patch every day
- History of malignancy of any organ system within the past 5 years unless patient is verified to be in stable condition with no active metastasis; history within the past year or current diagnosis of cerebrovascular disease
- The use of the following treatments prior to study enrollment were restricted:
    - Succinylcholine-type muscle relaxants or lithium within the prior 2 weeks
    - Cholinesterase inhibitors and other approved AD treatments within the prior 2 weeks, with exception of stable treatment with memantine for at least the prior 3 months

- Investigational drugs or any treatment known to cause major organ system toxicity within the prior 4 weeks; any new psychotropic medication or dopaminergic agent if not taken at a stable dose within the prior 4 weeks

- Centrally acting anticholinergic drugs including tricyclic and tetracyclic antidepressants, or peripheral anticholinergics, if not taken at a stable dose during the prior 4 weeks

5.3.1.6.3 Eligibility Criterion for Entry into the Double-Blind Phase

At Weeks 24, 36, and 48 (IOL phase) patients were evaluated for cognitive decline, which was defined as a MMSE decline of ≥ 2 points from the previous visit OR at ≥ 3 points from IOL baseline. The clinical judgment of the investigator that the patient has experienced some degree of functional decline in addition to cognitive decline was also required.

Patients meeting these criteria were randomized to the DB phase, and those who did not meet the criteria by IOL-Week 48 continued into the EOL.

5.3.1.7 Dosage

Patients enrolled into the IOL phase were started on Exelon 5 cm^2 patch daily for 4 weeks and subsequently titrated to Exelon 10 cm^2 patch daily for a total treatment period of 24 to 48 weeks.

Patients enrolled in the DB phase were randomized equally to 1 of 2 treatment groups:

- Exelon 10 cm^2 patch once daily and placebo matched 15 cm^2 patch once daily, or

- Exelon 15 cm^2 patch once daily and placebo matched 10 cm^2 patch once daily

Patients who did not demonstrate the required functional (investigator assessment) and cognitive (MMSE) decline by Week 48 of the IOL were offered continuing treatment with Exelon 10 cm^2 patch in an EOL phase.

5.3.1.8 Schedule

The following graphics, copied from the submission, summarize the schedules of study procedures for each of the respective study periods:

Table 9-2 Evaluation schedule: Screening and IOL phase

Period	Screening		IOL treatment						
	Screening	Baseline	Titration	Maintenance					
Week	-5 to -1	0	4	8	12	24	36*	48*	PD
Visit	1	2	3	4	5	6	7	8	
Screening information									
Screening log / informed consent	X								
Inclusion/exclusion criteria; DSM-IV criteria for dementia of the Alzheimer's type; and NINCDS/ADRDA criteria for probable AD	X	X							
MRI / CT scan	X[2]								
Lab. diagnostic screening tests; Physical and /neurological exam	X[3]	X[4]							
ECG	X	X[4]				X[5]	X[5]	X[5]	X
Assessment of fertility (Canada only) #	X								
Demography and background information; Prior use of AChE inhibitor treatment	X								
Medical history/current conditions	X	X							
Drug dispensing label		X	X	X	X	X	X	X	
Dosage administration record; treatment compliance			X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
MMSE	X	X			X	X	X	X	X
Decline criteria						X	X	X	X
ADAS-cog; ADCS-Instrumental ADL; Trail Making Test (Parts A and B); NPI-10		X				X[5]	X[5]	X[5]	X
Adverse events			As needed						
Serious adverse events	As needed								
Vital signs	X	X	X	X	X	X	X	X	X
Laboratory tests	X	X[4]						Canada X X	
Caregiver Medication Questionnaire		X				X			X
BuChE-K and APOE-ε4[6]		X							
Inflammatory biomarkers[6]		X				X[5]	X[5]	X[5]	X
Study phase completion						X[5]	X[5]	X[5]	
Intermediate Home/ Assisted Living Quest.; Study Completion Form									X

SCR = screening BL = baseline IOL = initial open-label

* Visit performed only in patients who did not demonstrate cognitive decline at previous visit.

[(Canada only) # Only to be performed in female patients aged 50-55].

2 Conducted within at least 2 years prior to the baseline visit.

3 Performed only if not tested within the past 12 months prior to the baseline visit.

4 Repeated only if screening values were abnormal or if > 5 weeks have elapsed since screening

5 Conducted at V8 for non-declining patients and at last visit prior to randomization, for declining patients

6 Analyzed by central laboratory

Table 9-3 Assessment schedule double-blind phase for decliners

Period	Double-blind phase for decliners							
	Maintenance							
Week	**4**	**8**	**12**	**16**	**24**	**32**	**36**	**48/PD**
Visit	**V 1.1**		**V 1.2**		**V 1.3**		**V 1.4**	**V 1.5**
Telephone contact		**2.1**		**2.2**		**2.3**		
Drug dispensing label	X		X		X		X	
Dosage administration record; concomitant medications; treatment compliance	X		X		X		X	X
ADAS-cog subscale			X		X			X
ADCS-Instrumental ADL subscale		X	X	X	X	X		X
Trail Making Test (Parts A and B)					X			X
NPI-10								X
ECG; Physical/ neurological exam								X
Adverse events; serious adverse events	As needed							
Vital signs and weight	X		X		X		X	X
Laboratory tests (Canada only)			X[3]		X[4]			X
Inflammatory biomarkers[1]								X
Intermediate Home/ Assisted Living Quest.								X
Study completion form								X

1 Analyzed by central laboratory

[(Canada only) 3 To be conducted only for patients randomized at Visit 7]

[(Canada only) 4 To be conducted only for patients randomized at Visit 6]

Table 9-4 Assessment schedule extended open-label treatment for non-decliners

Period	Open-label treatment for non-decliners			
	Maintenance			
Week	**12**	**24**	**36**	**48/PD**
Visit	**V 3.1**	**V 3.2**	**V 3.3**	**V 3.4**
Drug dispensing label	X	X	X	
Dosage administration record; concomitant medications; treatment compliance	X	X	X	X
ADAS-cog; ADCS-Instrumental ADL; Trail Making Test (Parts A and B); NPI-10				X
Physical/ neurological exam; ECG				X
Adverse events and serious adverse events	As needed			
Vital signs and weight	X	X	X	X
Intermediate home/ assisted living questionnaire				X
Study completion form				X

5.3.1.9 Outcome Measures

5.3.1.9.1 Primary Efficacy Measures

The co-primary efficacy variables were the change from DB randomization baseline to DB Week 48 in the ADAS-cog total score and the ADCS-Instrumental ADL score.

5.3.1.9.2 Secondary Efficacy Measures

Secondary efficacy outcome measures included:

- ADCS-IADL (time to functional decline in the DB phase)
- Trail Making Test (TMT) Parts A and B
- 10-item Neuropsychiatric Inventory (NPI)

5.3.1.9.3 Exploratory Efficacy Measures

Exploratory efficacy outcome measures included:

- Systemic inflammatory markers
- Effect of BuChE wt/wt genotype

5.3.1.9.4 Safety Measures

Safety outcome measures included adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, 12-lead electrocardiograms (ECGs), vital signs, and body weights.

Due to the fact that laboratory abnormalities have not been associated with any of the currently marketed formulations of Exelon®, the current trial did not include regular assessments of any laboratory safety parameters beyond those obtained at the Screening and Baseline visits.

5.3.1.9.5 Pharmacokinetic Measures

Not applicable.

5.3.1.10 Description of Primary Efficacy Measures

5.3.1.10.1 Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog)

The ADAS-cog subscale is comprised of 11 items that are summed to a total score ranging from 0 to 70, with lower scores indicating less severe impairment. In the current trial, the test was administered by a mental health professional (e.g., M.D., Ph.D., Pharm.D., R.N., or equivalent qualifications) who had a minimum of 2 years research experience, and had achieved certification after completing rater training.

5.3.1.10.2 Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living (ADCS-IADL)

The ADCS-ADL scale is a caregiver-based scale composed of 23 items developed for use in dementia clinical studies. It is designed to assess the patient's performance of both basic and instrumental activities of daily living, however, in this study only the ADCS-Instrumental ADL (items 7-23) was used. The ADCS-Instrumental ADL total score ranged from 0 to 56, with higher scores indicating less severe impairment. The ADCS-Instrumental ADL subscale assesses activities such as those necessary for communicating and interacting with other people, maintaining a household, and conducting hobbies and interests.

5.3.1.11 Safety Monitoring

Adverse events, vital signs, physical examinations, basic neurological examinations, and electrocardiograms, were assessed according to the above schedule of study procedures.

5.3.1.12 Analysis Plan

5.3.1.12.1 General

Unless otherwise specified, all statistical tests were conducted at the 0.05 level of significance (two-sided), and the treatment effect will be analyzed using an ANCOVA model.

All efficacy analyses will be conducted in the ITT-DB population with LOCF and repeated on the ITT-DB with OC and PP-DB with LOCF and with OC as supportive analyses.

Definitions and conventions for handling efficacy and safety data are specified in the analysis plan.

5.3.1.12.2 Study Populations

5.3.1.12.2.1 Open-Label Treatment Phase

The Intent-To-Treat population in the Open-label Treatment Phase (ITT-OL) will consist of all patients who received at least one dose of study drug and had a baseline and at least one post-baseline efficacy assessment during the OL phase.

The Safety population in the Open-label Treatment Phase (Safety-OL) will consist of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment during the open-label phase. This population will also include the patients who are not randomized and continue with the extended open-label treatment after the initial Open Label Treatment Phase.

5.3.1.12.2.2 Double-Blind Treatment Phase

The All Randomized population will consist of all patients that are randomized to one of the treatment groups.

The Per Protocol population in the Double-blind Treatment Phase (PP-DB) will consist of all patients who are randomized, received at least one dose of study drug in the Double-blind Treatment Phase, and had at least one post-randomization assessment of the primary efficacy variable on the target dose.

The Intent-to-Treat population in the Double-blind Treatment Phase (ITT-DB) will consist of all patients who are randomized, received at least one dose of study drug in the Double-blind Treatment Phase, and had at least one post-randomization assessment of the primary efficacy variable. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization.

The Safety population in the Double-blind Treatment Phase (Safety-DB) will consist of all patients who are randomized, received at least one dose of study drug in the DB Treatment

Phase and had at least one post-randomization safety assessment during the double-blind phase. Patients will be analyzed according to treatment received. Of note, the statement that a patient had no adverse events also constitutes a safety assessment.

5.3.1.12.3 Disposition

The disposition of all study subjects is to be summarized in tables indicating the number and percentage of the following in each treatment group:

- Randomized
- In each analysis population
- Prematurely discontinued

5.3.1.12.4 Demographic and Baseline Characteristics

Descriptive statistics for background and demographic characteristics will be summarized separately for Open-label and Double-blind Treatment Phase. For the Double-blind Treatment Phase, they will be summarized by treatment.

5.3.1.12.5 Treatment Compliance

Treatment compliance is to be summarized using descriptive statistics and additional methods described in the submission.

5.3.1.12.6 Extent of Exposure

The number and percentage of patients exposed are provided for all phases as well as the summary statistics for the duration of exposure. For the Double-blind Treatment Phase, the information will be summarized by treatment group.

5.3.1.12.7 Prior and Concomitant Medications

The number and percentage of patients receiving concomitant medications and significant non-drug therapy will be summarized by preferred term (coded by World Health Organization [WHO] Anatomic Therapeutic Chemical classification [ATC]). Separate summaries will be prepared for Open-label and Double-blind Treatment Phase.

5.3.1.12.8 Primary Efficacy Parameters

The primary analysis is the difference between treatment arms from baseline to Week 48 of the DB treatment phase in the ADAS-cog and the ADCS-ADL.

The treatment groups will be compared using the least square means derived by an analysis of covariance (ANCOVA) model with the following explanatory variables: treatment, country, and last test score (for each respective scale) prior to randomization. The analysis will be based on the ITT-DB (LOCF), PP-DB (OC), and PP-DB (LOCF) populations.

The primary population for the confirmatory testing of the hypotheses will be the ITT-DB population. In case of missing values, the last available score will be used.

The above analysis will be tested at a two-sided significance level of 0.05. No adjustment for multiplicity is required since both hypotheses need to be simultaneously rejected to claim efficacy.

The primary analysis will also be performed for:

- PP-DB population with observed case (OC) values without imputing with a last observation on target dose carried forward approach (LOCF)

- ITT-DB population with LOCF imputation scheme to replace the missing values

The primary analysis for PP-DB with LOCF will also be performed using non-parametric methods such as the van Elteren test stratified by country to assess the robustness of the results.

5.3.1.12.9 Secondary Efficacy Parameters

5.3.1.12.9.1 Time to Functional Decline

Time to functional decline on the ADCS-IADL scale will be assessed over the DB treatment phase. Decline will be defined by either an at least one point decrease in a visit and confirmed by the following visit/assessment or at least two points decrease in the total score from DB randomization baseline.

Analysis of the time to functional decline will be performed using the log-rank test for interval censored data. Kaplan-Meier (KM) estimates of cumulative decline-free survival probabilities will be plotted versus time. The analysis will be on the ITT-DB (OC) population. The analysis will also be performed using the PP-DB (OC) population.

5.3.1.12.9.2 Trail Making Test (Parts A and B)

The change from DB randomization to Week 48 in total time to perform the Trailmaking Test A and B, respectively, will be assessed.

The treatment groups will be compared using least square means derived by an analysis of covariance model with the following explanatory variables: treatment, country, and the last total score prior to randomization. The analysis will be based on the PP-DB(LOCF), PPDB(OC) and ITT-DB(LOCF) populations.

5.3.1.12.9.3 Neuropsychiatric Inventory (NPI)

The change from DB randomization to Week 48 in the NPI will be assessed.

The treatment groups will be compared using least square means derived by an analysis of covariance model with the following explanatory variables: treatment, country, and the last NPI-10 total score prior to randomization. The analysis will be based on the PP-DB (LOCF), PP-DB (OC) and ITT-DB (LOCF) populations.

5.3.1.12.9.4 Mini Mental State Examination (MMSE)

The change from baseline in MMSE total score of 11 items will be summarized for the Open label Treatment Phase.

5.3.1.12.10 Subgroup Analyses

Analyses will be repeated within the subgroups as defined by age, specific symptoms, disease severity, genotype, and presence of elevated inflammatory markers for ADAS-Cog and ADCS Instrumental ADL.

5.3.1.12.11 Safety Parameters

The safety and tolerability variables to be evaluated are the frequency of adverse events, serious adverse events, GI adverse events, the discontinuation rate due to an AE, proportion of markedly abnormal values and the change from baseline for ECGs and vital signs.

Descriptive summary tables by treatment group will be presented for the safety and tolerability variables for the Double-blind Treatment Phase. Separate summaries will be provided for the Open-label Treatment Phase.

5.3.1.12.12 Pharmacokinetic Parameters

Not applicable.

5.3.1.12.13 Sample Size Rationale

The study protocol provides the following rationale for the sample size selected for the trial:

- Data from previous long-term Exelon® studies on the oral formulation suggest that the standard deviation of the change from baseline in ADAS-Cog score is approximately 8, and for the change from baseline in ADCS-Instrumental ADL score is also approximately 8. A slightly smaller treatment difference is assumed on the primary efficacy variable and co-primary efficacy variable when the primary analysis will be based on ITT population instead of PP population.

- A sample size of 410 patients in each group at the end of the Double-blind Treatment Phase will have 85% power to detect a treatment difference in means of 1.9 points on the ADAS-cog score and 1.9 points on the ADCS-Instrumental ADL score in the ITT population assuming that the common standard deviation is 8 for both the co-primary variables, using a two group t-test with a 0.050 two-sided significance level. A correlation of 0.35 between the co-primary outcome variables is assumed. To adjust for 5% of patients who may not be included in the ITT population, a total of 864 patients (432 per group) will be needed at the time of randomization (end of Open-label Treatment Phase).

- Even if the common SD of change from baseline in ADCS-Instrumental ADL is as high as 9, a total of 864 patients will be sufficient to provide 80% power to detect a treatment difference in means of 1.9 points on the ADCS-Instrumental ADL score in the ITT population.

- Based on the long-term study on Exelon® capsules and data from the ongoing trial, it is assumed that the percent of patients who will show cognitive decline (at least 2 points decline in MMSE from previous visit OR at least 3 points decline in MMSE from baseline) in the initial pen-label Treatment Phase will be 55%. Thus, it is estimated that 1571 patients need to be enrolled in the Open-label Treatment Phase to ensure that at least 864 declining patients will be available for randomization.

5.3.1.12.14 Interim Analysis

Not applicable.

5.3.1.13 Results

5.3.1.13.1 Data Sets Analyzed

The following table, copied from the submission, outlines the number of patients that were included in the analysis sets for each of the trial's phases:

Table 11-1 Number (%) of patients in analysis populations, by treatment

Population			Total n (%)
Open-label phases (Exelon 10 cm^2 treatment)			
Enrolled			1584 (100.0)
Safety - initial open-label (SAF-IOL)			1582 (99.9)
Intent to treat - initial open-label (ITT-IOL)			1518 (95.8)
Safety - extended open-label (SAF-EOL)			457 (28.9)
Intent to treat - extended open-label (ITT-EOL)			416 (26.3)
Double-blind treatment phase	**Exelon 15 cm^2 n (%)**	**Exelon 10 cm^2 n (%)**	**Total n (%)**
Randomized to the double-blind phase	280 (100.0)	287 (100.0)	567 (100.0)
Intent to treat - double-blind (ITT-DB)	265 (94.6)	271 (94.4)	536 (94.5)
Safety - double-blind (SAF-DB)	280 (100.0)	283 (98.6)	563 (99.3)
Per protocol - double-blind (PP-DB)	194 (69.3)	214 (74.6)	408 (72.0)

For the open-label phases, the percentages (%) are calculated based on the Enrolled population.
For the double-blind phase, the percentages (%) are calculated based on the Randomized population.
Source: PT-Table 14.1-2.1

There were no major differences observed between the treatment groups in the study's double-blind treatment phase in any of the various analysis sets.

It is notable that both of the treatment arms in the trial's DB phase enrolled significantly fewer subjects than was originally called for in the analysis plan (410 planned per arm versus 280 and 283 enrolled).

5.3.1.13.2 Demographics and Baseline Characteristics

The following two tables, copied from the submission, outline the patient demographic and background characteristics, respectively, for subjects in the enrolled population as displayed by decline status:

Table 11-2 Patient demographic characteristics, by decline status (Enrolled population)

Demographic Characteristic Category / statistic		Decliners N = 567 n (%)	Non-decliners N = 459 n (%)	Discontinued N = 558 n (%)	Total N = 1584 n (%)
Gender - n (%)	Male	200 (35.3)	194 (42.3)	198 (35.5)	592 (37.4)
	Female	367 (64.7)	265 (57.7)	360 (64.5)	992 (62.6)
Race - n (%)	Caucasian	548 (96.6)	442 (96.3)	522 (93.5)	1512 (95.5)
	Black	10 (1.8)	9 (2.0)	23 (4.1)	42 (2.7)
	Oriental	3 (0.5)	1 (0.2)	3 (0.5)	7 (0.4)
	Other	6 (1.1)	7 (1.5)	10 (1.8)	23 (1.5)
Age (years)	n	567	459	558	1584
	Mean (SD)	74.50 (7.056)	74.63 (6.957)	75.62 (7.309)	74.93 (7.131)
	Median	76.00	76.00	77.00	76.00
	Range	51.0 - 85.0	52.0 - 85.0	50.0 - 85.0	50.0 - 85.0
Age group - n (%)	< 65 years	58 (10.2)	44 (9.6)	53 (9.5)	155 (9.8)
	≥ 65 years	509 (89.8)	415 (90.4)	505 (90.5)	1429 (90.2)
Weight (kg)	n	566	458	558	1582
	Mean (SD)	68.74 (14.582)	70.27 (14.610)	68.83 (13.590)	69.21 (14.255)
	Median	68.00	70.00	67.50	68.10
	Range	39.0 - 121.0	40.5 - 119.0	41.0 - 124.3	39.0 - 124.3
Weight category (kg) - n (%)	< 50	46 (8.1)	25 (5.4)	34 (6.1)	105 (6.6)
	50 to 80	410 (72.3)	330 (71.9)	423 (75.8)	1163 (73.4)
	> 80	110 (19.4)	103 (22.4)	101 (18.1)	314 (19.8)
BMI (kg/m^2)	n	561	451	553	1565
	Mean (SD)	25.73 (4.555)	25.95 (4.413)	25.77 (4.372)	25.81 (4.448)
	Median	25.30	25.70	25.30	25.40
	Range	16.1 - 50.4	12.9 - 40.2	17.2 - 46.1	12.9 - 50.4

Demographic information was collected on the day of screening (Visit 1). Weight was collected at the initial open-label (IOL) baseline which is the last assessment on/or before Visit 2.

N: Number of patients in the Enrolled population.
n: Number of patients meeting the criterion (for categorical variables); number of patients with a non-missing assessment (for continuous variables).
Body Mass Index (BMI) = weight (kg) / height (m) ^{2}.

No major differences were noted between these groups outside of the observation that a somewhat higher percentage of males was evident in the non-decliner group (42.3%) as compared to both the decliner (35.3%) and the discontinued (35.5%) groups. It is unlikely that this difference would affect the analysis and/or interpretation of the study's findings in any significant manner.

Table 11-3 Patient background characteristics by decline status (Enrolled population)

Background characteristics Category / statistic		Decliners N = 567	Non-decliners N = 459	Discontinued N = 558	Total N = 1584
Patient's relatives with AD - n (%)	Mother	98 (17.3)	89 (19.4)	77 (13.8)	264 (16.7)
	Father	40 (7.1)	29 (6.3)	30 (5.4)	99 (6.3)
	Sibling	75 (13.2)	57 (12.4)	82 (14.7)	214 (13.5)
	Other	53 (9.3)	27 (5.9)	36 (6.5)	116 (7.3)
	None	361 (63.7)	293 (63.8)	380 (68.1)	1034 (65.3)
Time since first symptom of AD was noticed by patient/caregiver (years) [(a)]	n	567	459	558	1584
	Mean (SD)	4.09 (2.779)	3.40 (2.553)	3.93 (2.877)	3.84 (2.764)
	Median	3.40	2.70	3.10	3.10
	Range	0.2 - 17.7	0.1 - 19.2	0.4 - 19.4	0.1 - 19.4
Time since first symptom of AD was first diagnosed by physician (years) [(a)]	n	567	459	558	1584
	Mean (SD)	1.92 (1.988)	1.40 (1.692)	1.74 (2.012)	1.71 (1.927)
	Median	1.30	0.70	1.00	1.00
	Range	0.0 - 12.6	0.0 - 10.3	0.0 - 11.9	0.0 - 12.6
Number of years of formal education	n	566	459	558	1583
	Mean (SD)	10.6 (3.97)	10.2 (4.01)	10.8 (4.24)	10.5 (4.08)
	Median	11.0	10.0	12.0	11.0
	Range	2.0 - 22.0	0.0 - 23.0	2.0 - 25.0	0.0 - 25.0
Mini Mental State Examination	n	567	459	558	1584
	Mean (SD)	16.9 (3.60)	18.8 (3.25)	17.8 (3.40)	17.8 (3.52)
	Median	17.0	19.0	18.0	18.0
	Range	10.0 - 25.0	10.0 - 24.0	10.0 - 24.0	10.0 - 25.0
Patient's living situation-n (%)					
Living alone		61 (10.8)	64 (13.9)	79 (14.2)	204 (12.9)
Living with caregiver or other		491 (86.6)	389 (84.7)	459 (82.3)	1339 (84.5)
Assisted living/ group home		15 (2.6)	6 (1.3)	20 (3.6)	41 (2.6)
Patients meeting criteria of probable dementia with Lewy bodies - n (%)	Yes	14 (2.5)	21 (4.6)	23 (4.1)	58 (3.7)
	No	553 (97.5)	438 (95.4)	535 (95.9)	1526 (96.3)
Previous AChEI use-n (%)	Yes	351 (61.9)	206 (44.9)	303 (54.3)	860 (54.3)
	No	216 (38.1)	253 (55.1)	255 (45.7)	724 (45.7)
Previous ChEI use - n (%)	Yes	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
	No	567 (100.0)	458 (99.8)	558 (100.0)	1583 (99.9)
Previous use of other approved AD treatment - n (%)	Yes	208 (36.7)	95 (20.7)	156 (28.0)	459 (29.0)
	No	359 (63.3)	364 (79.3)	402 (72.0)	1125 (71.0)

AchEI = Acetycholinesterase Inhibitor ChEI = Cholinesterase Inhibitor AD = Alzheimer's disease
MMSE = Mini Mental State Examination
N: Number of patients in the Enrolled population.
n: Number of patients meeting the criterion (for categorical variables); number of patients with a non-missing assessment (for continuous variables).
Background characteristics at initial open-label (IOL) baseline which is the last assessment on/or before Visit 2.
(a) Time since first symptom of AD is calculated with respect to IOL baseline visit.

When compared to the non-decliners, patients who were decliners were more likely to have had a greater time at study entry since the appearance of AD symptoms (median of 3.4 versus 2.70 years) and a formal diagnosis of AD by a physician (median of 1.30 versus 0.70 years). Decliners were also likely to have lower baseline MMSE scores compared to non-decliners (16.9 ± 3.6 versus 18.8 ± 3.3). Additionally, decliners were less likely to be living alone (10.8%) as compared to non-decliners (13.9%) and were also more likely to have used a cholinesterase inhibitor in the past (61.9 versus 44.9%, respectively) or other AD treatment (36.7 versus 20.7, respectively).

These findings are consistent with the clinical expectation that patients with somewhat more advanced disease would be more likely to experience greater clinical decline during the 24-48 weeks of the study's IOL phase. As these subjects were subsequently randomized into the trial's double-blind phase, these differences would not be expected to affect the final interpretation of the trial data.

The following table, copied from the submission, outlines the demographic characteristics of the patient groups in the double-blind randomized treatment phase of the trial:

Table 11-4 Patient demographic characteristics by treatment group (Randomized population)

Demographic Characteristic Category / statistic		Exelon 15 cm^2 N = 280	Exelon 10 cm^2 N = 287	Total N = 567
Gender - n (%)	Male	95 (33.9)	105 (36.6)	200 (35.3)
	Female	185 (66.1)	182 (63.4)	367 (64.7)
Race - n (%)	Caucasian	266 (95.0)	282 (98.3)	548 (96.6)
	Black	8 (2.9)	2 (0.7)	10 (1.8)
	Oriental	2 (0.7)	1 (0.3)	3 (0.5)
	Other	4 (1.4)	2 (0.7)	6 (1.1)
Age (years)	n	280	287	567
	Mean (SD)	75.61 (7.365)	75.88 (6.787)	75.74 (7.073)
	Median	77.50	77.00	77.00
	Range	54.0 - 87.0	53.0 - 87.0	53.0 - 87.0
Age group - n (%)	< 65 years	34 (12.1)	18 (6.3)	52 (9.2)
	≥ 65 years	246 (87.9)	269 (93.7)	515 (90.8)
Weight (kg)	n	280	287	567
	Mean (SD)	69.47 (15.501)	67.93 (13.893)	68.69 (14.716)
	Median	69.35	67.00	68.00
	Range	38.0 - 118.4	40.0 - 110.6	38.0 - 118.4
Weight category (kg) - n (%)	< 50	27 (9.6)	24 (8.4)	51 (9.0)
	50 to 80	193 (68.9)	209 (72.8)	402 (70.9)
	> 80	60 (21.4)	54 (18.8)	114 (20.1)
BMI (kg/m^2)	n	279	282	561
	Mean (SD)	25.98 (4.776)	25.42 (4.407)	25.70 (4.599)
	Median	25.60	24.90	25.30
	Range	16.4 - 49.3	16.0 - 44.8	16.0 - 49.3

N = Number of patients in the Randomized population.
n = Number of patients meeting the criterion (for categorical variables) or the number of patients with a non-missing assessment (for continuous variables).
Body Mass Index (BMI) = weight (kg) / height (m) ^{2}.
Demographic characteristics at double-blind baseline, which is the last assessment in the initial open-label phase are presented.

Overall there was an approximately 2-fold higher percentage of females in both treatment arms which is not unexpected or particularly relevant to the final interpretation of trial data. The overwhelming majority of subjects were Caucasian which also would not be expected to have a major impact on the trial's results. The Exelon 15cm^2 treatment arm did have a higher percentage of subjects who were less than 65 years of age (12.1 versus 6.3%), however the overall number of subjects was small (34 versus 18) and would therefore not be expected to impact the trial results. There did not appear to be any meaningful differences on other demographic differences between treatment groups.

The following table, also copied from the submission, summarizes the background characteristics of subjects in the double-blind phase of the trial by treatment group:

Table 11-5 Patient background characteristics, by treatment group (Randomized population)

Background characteristics Category / statistic		Exelon 15 cm^2 N = 280	Exelon 10 cm^2 N = 287	Total N = 567
Patient's relatives with AD - n (%)	Mother	49 (17.5)	49 (17.1)	98 (17.3)
	Father	19 (6.8)	21 (7.3)	40 (7.1)
	Sibling	38 (13.6)	37 (12.9)	75 (13.2)
	Other	28 (10.0)	25 (8.7)	53 (9.3)
	None	175 (62.5)	186 (64.8)	361 (63.7)
Time since first symptom of AD was noticed by patient/caregiver (years) [a]	n	280	287	567
	Mean (SD)	3.86 (2.780)	4.31 (2.765)	4.09 (2.779)
	Median	3.20	3.60	3.40
	Range	0.2 - 17.7	0.3 - 15.6	0.2 - 17.7
Time since first symptom of AD was first diagnosed by physician (years) [a]	n	280	287	567
	Mean (SD)	1.80 (1.821)	2.04 (2.136)	1.92 (1.988)
	Median	1.25	1.40	1.30
	Range	0.0 - 10.9	0.0 - 12.6	0.0 - 12.6
Number of years of formal education	n	279	287	566
	Mean (SD)	10.5 (3.97)	10.6 (3.99)	10.6 (3.97)
	Median	12.0	11.0	11.0
	Range	2.0 - 20.0	3.0 - 22.0	2.0 - 22.0
MMSE [b]	n	280	287	567
	Mean (SD)	14.1 (4.79)	14.2 (4.58)	14.2 (4.68)
	Median	14.0	14.0	14.0
	Range	0.0 - 24.0	2.0 - 26.0	0.0 - 26.0
Time to meet decline criteria in IOL -n (%)	≤ 36 weeks	140 (50.0)	147 (51.2)	287 (50.6)
	> 36 weeks	140 (50.0)	140 (48.8)	280 (49.4)
Patient's living situation-n (%)				
Living alone		29 (10.4)	32 (11.1)	61 (10.8)
Living with caregiver or other		244 (87.1)	247 (86.1)	491 (86.6)
Assisted living/ group home		7 (2.5)	8 (2.8)	15 (2.6)
Patients who met criteria of probable dementia with Lewy bodies - n (%)	Yes	6 (2.1)	8 (2.8)	14 (2.5)
	No	274 (97.9)	279 (97.2)	553 (97.5)
Previous AChEI use-n (%)	Yes	166 (59.3)	185 (64.5)	351 (61.9)
	No	114 (40.7)	102 (35.5)	216 (38.1)
Previous use of other approved AD treatments - n (%)	Yes	105 (37.5)	103 (35.9)	208 (36.7)
	No	175 (62.5)	184 (64.1)	359 (63.3)

AchEI - Acetycholinesterase inhibitor AD - Alzheimer's disease IOL - initial open-label phase

MMSE - Mini Mental State Examination

N is the number of patients in the Randomized population.
n is the number of patients meeting the criterion (for categorical variables); number of patients with a non-missing assessment (for continuous variables).

(a) Time since first symptom of AD is calculated with respect to IOL-baseline visit.
(b) MMSE at double-blind (DB) baseline.

Background characteristics at DB baseline which is the last assessment in the IOL phase are presented.

There were no apparent meaningful differences between treatment groups in any of the baseline characteristics that have been outlined in the preceding table.

The submission notes that at DB-baseline approximately 20% of subjects had MMSE scores below 10 while at IOL-baseline only 1 subject had an MMSE score below 10. However, as both the mean and median MMSE scores were comparable between treatment groups, it is unlikely that this difference was meaningful.

The treatment groups were also compared on a series of components of medical history and prior medications. There were slightly higher rates of metabolic (51.4 versus 46.3%), cardiac (22.1 versus 19.5%), and vascular histories (61.4 versus 55.7%) in the 15 cm^2 group versus the 10 cm^2 group. Hypertension specifically was observed somewhat more frequently in the 15 cm^2 group (56.8 versus 51.2%). These conditions are well-known to be intercurrent in this population and the between-group differences are generally not great. Furthermore, the generally consistent, albeit small, trend of a greater frequency of these conditions in the 15 cm^2 group would arguably be congruent with publications that suggest that a higher rate of background cerebrovascular pathology and/or risk factors may predict a more rapid rate of the clinical progression of AD. Regardless, it is not expected that these differences would meaningfully affect the interpretation of the trial's results.

5.3.1.13.3 Protocol Deviations

The following table, copied from the submission, summarizes the protocol deviations for the DB phase of the trial:

Number (%) of patients with protocol deviations in the double blind phase, by treatment group
(Randomized population)

	Exelon 15 cm2 N=280 n (%)	Exelon 10 cm2 N=287 n (%)	Total N=567 n (%)
At least one protocol deviation	31 (11.1)	22 (7.7)	53 (9.3)
Major protocol deviations	1 (0.4)	0 (0.0)	1 (0.2)
Decline criteria not met at randomization	1 (0.4)	0 (0.0)	1 (0.2)
Other deviations			
Drug dispensing error	2 (0.7)	2 (0.7)	4 (0.7)
Incorrect study medication taken or incorrect daily dose taken	5 (1.8)	0 (0.0)	5 (0.9)
Incorrect titration/retitration of study medication	5 (1.8)	0 (0.0)	5 (0.9)
Missing or not done key efficacy evaluation for completed scheduled visit (ADAS-Cog or ADCS-IADL)	17 (6.1)	16 (5.6)	33 (5.8)
Missing or not done safety evaluation for non-missing scheduled visit	6 (2.1)	4 (1.4)	10 (1.8)
Use of or change in restricted medication after OL baseline	2 (0.7)	0 (0.0)	2 (0.4)

As the table indicates, only 1 subject (0204/00004) had a major protocol deviation. This subject did not meet the protocol defined decline criteria as the decline criteria were mistakenly applied to a comparison to Visit 1 and not Baseline. The remainder of the observed deviations were

infrequent, generally comparable between groups, and not likely to affect the interpretability of the trial's findings.

5.3.1.13.4 Efficacy Results

5.3.1.13.4.1 Primary Efficacy Results

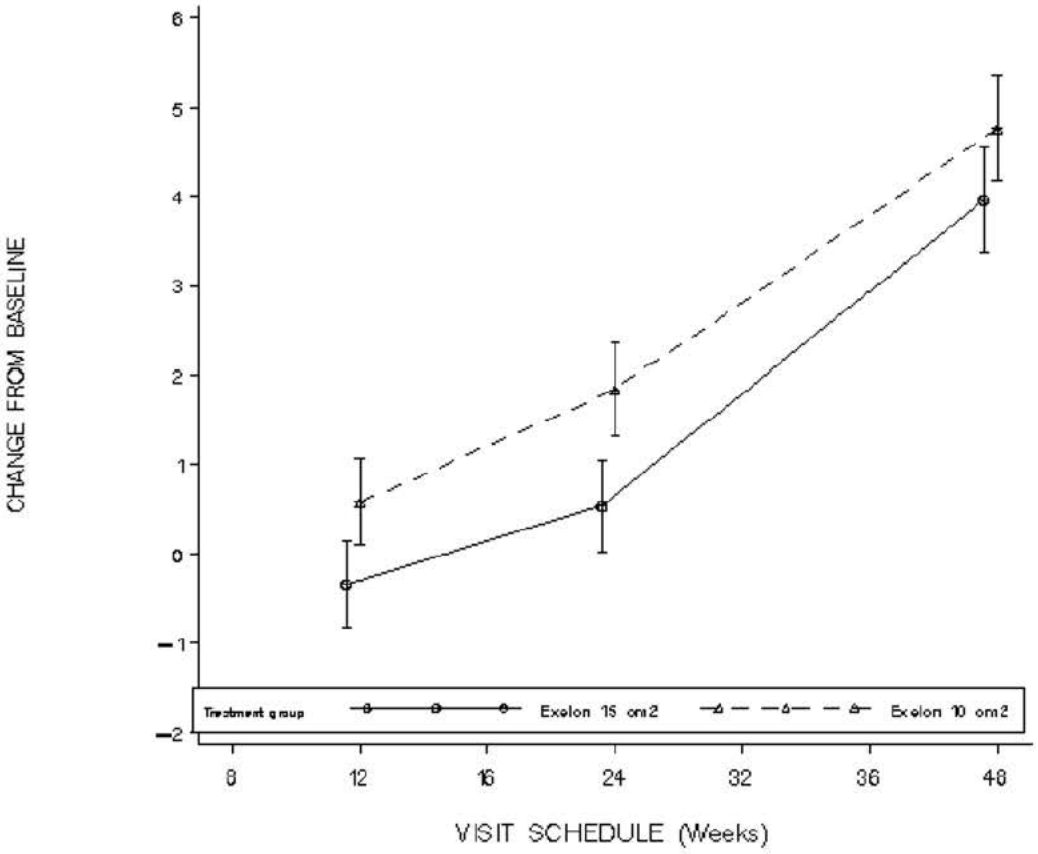
The trial's assessment of efficacy was primarily based on the results of the analysis of the two co-primary outcome measures, namely: change from DB-baseline (randomization) to DB-Week 48 in cognition and function as assessed by the ADAS-cog and ADCS-Instrumental ADL subscales, respectively, in the ITT-DB population with LOCF.

The analyses of the co-primary endpoints were based on an ANCOVA model adjusted for country and baseline score in the ITT-DB population with LOCF and were repeated on the ITT-DB with OC and PP-DB with LOCF and with OC as supportive analyses.

5.3.1.13.4.1.1 ADAS-Cog

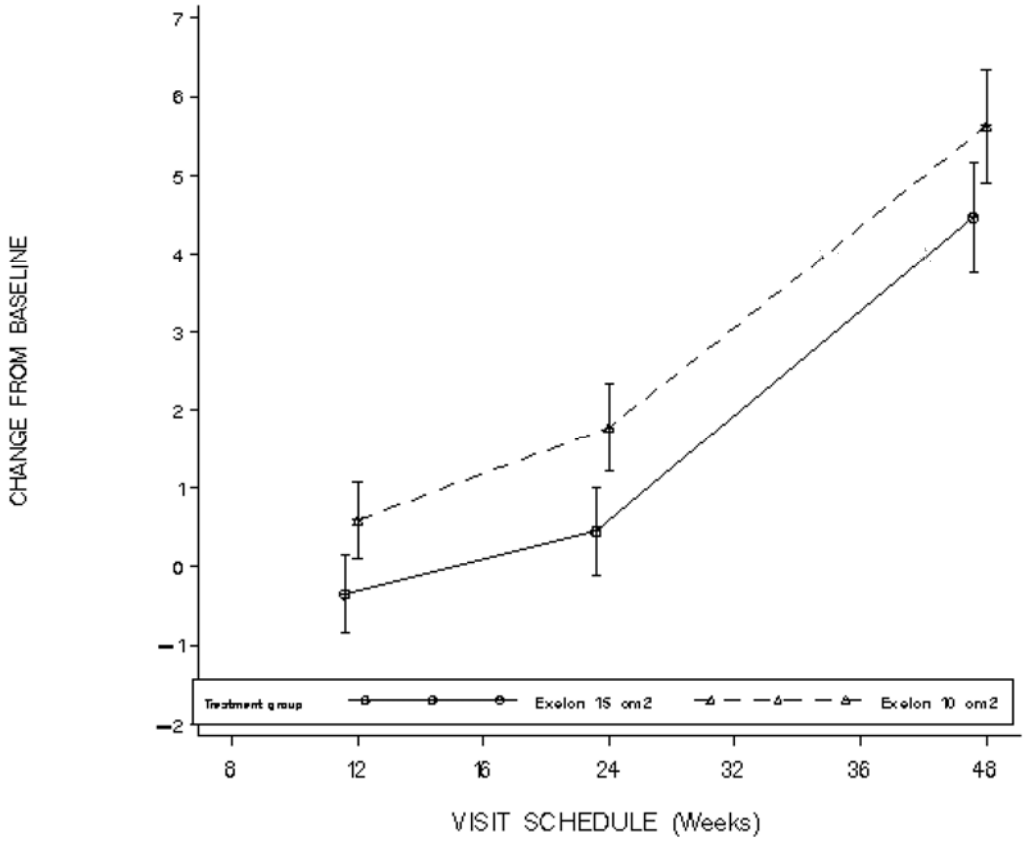
The following graphics, copied from the submission, display the results of the ADAS-Cog score change from baseline (as determined by the ANCOVA analysis described previously) for the ITT-LOCF (the primary outcome assessment) and the ITT-OC populations, respectively:

Figure 11-1 **ADAS-cog total scoreCog change from baseline (LSM (SEM)) in the double-blind phase, by treatment group (ITT-DB population, LOCF)**



A negative change indicates an improvement from baseline.
Least square means (LSM) and the standard errors of the LSM (SEM) are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADAS-cog score.
$p < 0.05$ at double-blind Week 24 for Exelon 15 cm^2 patch vs. Exelon 10 cm^2 patch.

Figure 11-2 ADAS-cog total scores change from baseline (LSM (SEM)) in the double-blind phase, by treatment group (ITT-DB population, OC)



A negative change indicates an improvement from baseline.
Least square means (LSM) and the standard errors of the LSM (SEM) are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADAS-cog score.
$p < 0.05$ at double-blind Week 24 for Exelon 15 cm^2 patch vs. Exelon 10 cm^2 patch.

The following table, copied from the submission, outlines the changes from baseline in ADAS-cog scores in the ITT-DB population (both the LOCF and OC groups, respectively):

Table 11-6 Change from baseline in ADAS-cog in the double-blind phase, by treatment group (ITT-DB population)

Population	Visit		Exelon 15 cm^2 N = 265		Exelon 10 cm^2 N = 271		Exelon 15 cm^2 - Exelon 10 cm^2		
			n	Mean	n	Mean	DLSM	95% CI	p-value
LOCF		Baseline	264	34.4	268	34.9			
	DB-Week 12	Value	264	34.2	268	35.5			
		Change	264	-0.2	268	0.6	-0.9	(-2.0, 0.1)	0.091
	DB-Week 24	Value	264	35.4	268	37.1			
		Change	264	1.0	268	2.2	-1.3	(-2.5, -0.2)	0.027*
	DB-Week 48	Value	264	38.5	268	39.7			
		Change	264	4.1	268	4.9	-0.8	(-2.1, 0.5)	0.227
OC	DB-Week 12	Baseline	259	34.2	265	34.8			
		Value	259	34.0	265	35.5			
		Change	259	-0.2	265	0.6	-0.9	(-2.0, 0.2)	0.091
	DB-Week 24	Baseline	238	34.2	238	34.5			
		Value	238	35.1	238	36.7			
		Change	238	0.9	238	2.1	-1.3	(-2.5, -0.1)	0.035*
	DB-Week 48	Baseline	211	33.9	193	33.4			
		Value	211	38.2	193	38.7			
		Change	211	4.3	193	5.3	-1.2	(-2.7, 0.4)	0.141

ADAS-cog - Alzheimer's disease assessment scale-cognitive subscale
ANCOVA - analysis of covariance CI - confidence interval DB - double-blind
DLSM - difference in lease square means IOL - initial open-label

ADAS-cog scores range from 0 to 70, with lower scores indicating less severe impairment.
A negative difference in DLSM indicates greater improvement in Exelon 15 cm^2 as compared to Exelon 10 cm^2.

n is the number of patients with an assessment at baseline (last assessment in the IOL phase and either the corresponding visit (for the OC) or with at least 1 post baseline assessment (for the LOCF).

The DLSM, 95% CI, and p-value are based on an ANCOVA model adjusted for country and baseline ADAS-cog score.
* $p < 0.05$

The most notable finding from the analysis of the ADAS-cog results is that in the DB-ITT LOCF population the difference in the treatment groups was not statistically significant at Week 48 which was the pre-specified primary outcome measure for this endpoint [DLSM of -0.8 (-2.1, 0.5) **p=0.227**]. The difference in ADAS-cog scores in the DB-ITT OC population was similarly not statistically significant at Week 48 [DLSM of -1.2 (-2.7, 0.4) p=0.141].

By virtue of these results it should be clearly stated at this point that the protocol did **not** successfully meet the pre-specified outcome criteria on one of the co-primary endpoints (ADAS-cog at Week 48 in the DB-ITT LOCF population).

The difference between treatment groups in the change from Baseline in ADAS-cog scores was, however, statistically significant at Week 24 [DLSM of -1.3 (-2.5, -0.2) p=0.027]. A similar result was found in the DB-ITT OC population [DLSM of -1.3 (-2.5, 0.1) p=0.035].

This statistically significant difference between treatment arms on the ADAS-cog at Week 24 remains worthy of further consideration. One factor which should be included in the interpretation of this result relates to the fact that the historical convention for the trial duration of

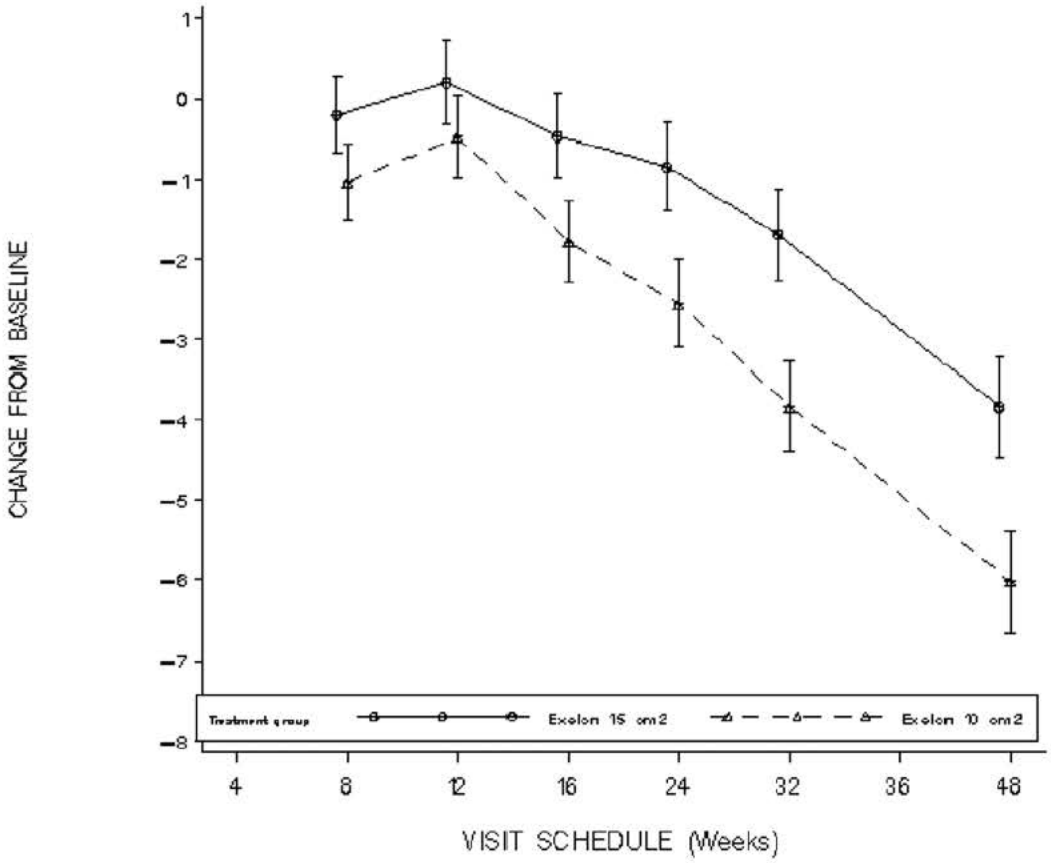
the currently approved (and presumably symptomatic) AD therapies is between 12-24 weeks. Therefore, the efficacy of any of these approved agents is also essentially unknown at 48 weeks of treatment. Additionally, Study D2340 is comparing the 15cm^2 patch size to an active comparator (the 10cm^2 patch) and not placebo which is a relatively important distinction. If, for example, these two doses were being compared against placebo in a standard parallel-group dose-ranging trial, even a complete lack of separation on this particular endpoint from each other (assuming both were superior to placebo) would not necessarily be an *a priori* barrier to approval in and of itself. In that instance, the entirety of the trial's results, including the additional efficacy endpoints and any dose-related safety findings, would also factor into any ultimate regulatory decision. When viewed in this context, the fact that the treatment arms statistically separated on the ADAS-cog at Week 24, albeit not at Week 48 which was the pre-specified endpoint, may still speak favorably to the overall approvability of the 15cm^2 dose.

Clearly a possible explanation for the loss of a statistically significant difference in the ADAS-cog score between the treatment arms between Weeks 24 and 48 may lie in the substantial number of subject dropouts observed in the trial (particularly since the effect sizes were approximately identical between these two timepoints). Specifically, the number of subjects with missing data during the DB phase of the study, who were therefore not included in the OC analysis for example, was fairly substantial. 54/265 subjects were excluded (relative to Baseline) from the Week 48 analysis in the 15 cm^2 treatment group and 78/271 subjects were excluded in the 10cm^2 treatment group. Furthermore, the number of subjects excluded from the ITT-LOCF population between Weeks 24 and 48 was particularly high at 29 and 45 in the 15cm^2 and 10cm^2 arms, respectively. It should be again mentioned here that the trial failed to reach the targeted initial enrollment of 410 subjects per treatment arm in the DB phase. While this rate of missingness may have certainly had an adverse affect on the study's ability to detect a difference on the ADAS-cog at Week 48 (as opposed to at Week 24), there is unfortunately no way to determine to what degree, or in what direction, this affect may have contributed to the trial's results.

5.3.1.13.4.1.2 ADCS-Instrumental ADL

The following graphics, copied from the submission, display the results of the ADCS-IADL score change from baseline (as determined by the ANCOVA analysis described above) for the ITT-LOCF (the primary outcome assessment) and the ITT-OC populations, respectively:

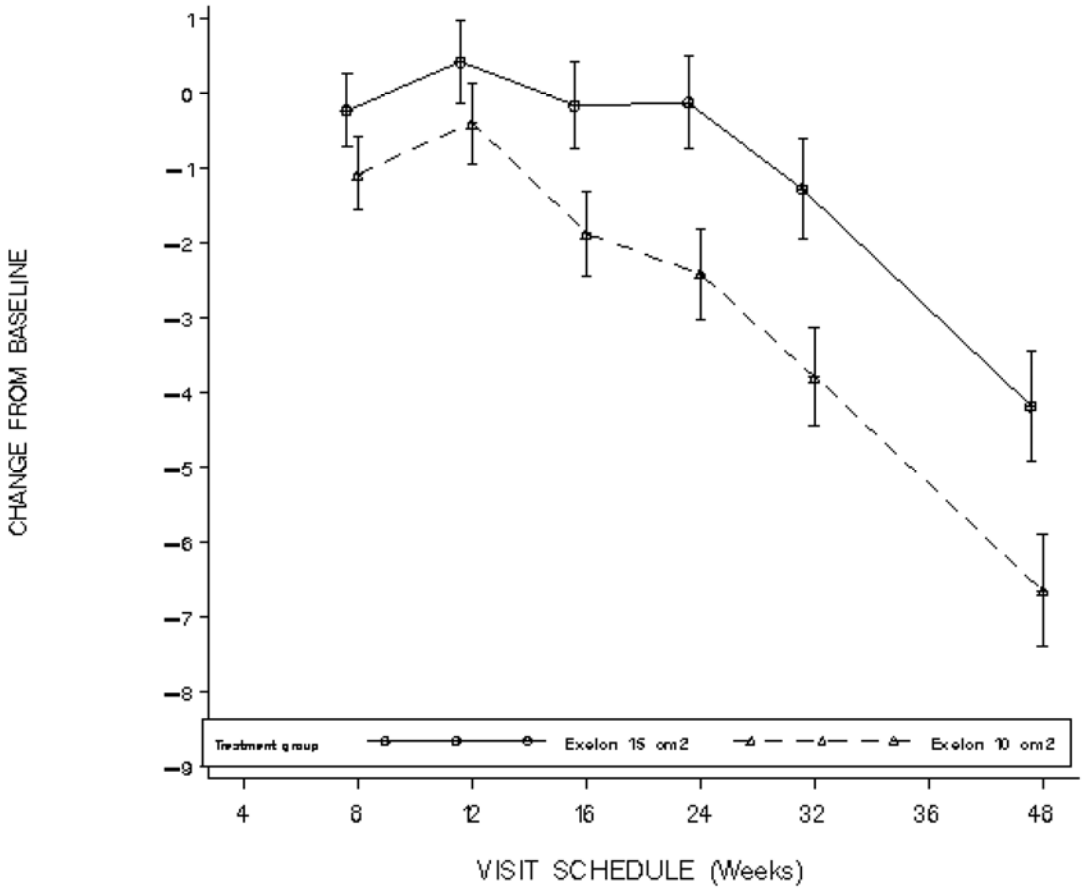
Figure 11-3 **ADCS-Instrumental ADL score change from baseline (LSM (SEM)) in the double-blind phase (ITT-DB population, LOCF)**



A positive change indicates an improvement from baseline.

Least square means (LSM) and the standard errors of the LSM (SEM) are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADCS-Instrumental ADL score.
$p < 0.05$ at double-blind Weeks 16, 24, 32, and 48 for Exelon 15 cm^2 patch vs. Exelon 10 cm^2 patch.

Figure 11-4 ADCS-Instrumental ADL score change from baseline (LSM (SEM)) in the double-blind phase (ITT-DB population)



A positive change indicates an improvement from baseline.

Least square means (LSM) and the standard errors of the LSM (SEM) are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADCS-Instrumental ADL score.
$p < 0.05$ at double-blind weeks 16, 24, 32, and 48 for Exelon 15 cm^2 patch vs. Exelon 10 cm^2 patch.

The follow table, copied from the submission, outlines the changes from baseline in ADCS-IADL scores in the ITT-DB population (both the LOCF and OC groups, respectively):

Table 11-7 Change from baseline in ADCS-Instrumental ADL in the double-blind phase, by treatment group (ITT-DB Population)

Population / Visit			Exelon 15 cm²		Exelon 10 cm²		Exelon 15 cm² - Exelon 10 cm²		
			n	Mean	n	Mean	DLSM	95% CI	p-value
LOCF		Baseline	265	27.5	271	25.8			
	Week 8	Value	265	27.3	271	25.0			
		Change	265	-0.2	271	-0.8	0.8	(-0.2, 1.9)	0.114
	Week 12	Value	265	27.5	271	25.4			
		Change	265	0.1	271	-0.4	0.7	(-0.5, 1.8)	0.252
	Week 16	Value	265	26.7	271	24.0			
		Change	265	-0.7	271	-1.8	1.3	(0.2, 2.5)	0.025*
	Week 24	Value	265	26.0	271	22.9			
		Change	265	-1.5	271	-2.8	1.7	(0.5, 2.9)	0.005*
	Week 32	Value	265	25.2	271	21.7			
		Change	265	-2.2	271	-4.0	2.1	(0.9, 3.4)	<0.001*
	Week 48	Value	265	23.1	271	19.6			
		Change	265	-4.4	271	-6.2	2.2	(0.8, 3.6)	0.002*
OC	Week 8	Baseline	257	27.5	261	26.0			
		Value	257	27.3	261	25.2			
		Change	257	-0.2	261	-0.8	0.8	(-0.2, 1.9)	0.122
	Week 12	Baseline	250	27.5	259	25.8			
		Value	250	27.7	259	25.4			
		Change	250	0.3	259	-0.3	0.8	(-0.4, 2.0)	0.174
	Week 16	Baseline	237	27.3	243	26.2			
		Value	237	26.8	243	24.2			
		Change	237	-0.5	243	-2.0	1.7	(0.5, 2.9)	0.006*
	Week 24	Baseline	232	27.8	243	26.3			
		Value	232	26.8	243	23.3			
		Change	232	-1.0	243	-3.0	2.3	(1.0, 3.6)	<0.001*
	Week 32	Baseline	221	27.5	222	26.8			
		Value	221	25.6	222	22.6			
		Change	221	-1.9	222	-4.2	2.5	(1.1, 3.9)	<0.001*
	Week 48	Baseline	209	27.9	198	27.6			
		Value	209	23.3	198	20.7			
		Change	209	-4.6	198	-6.9	2.5	(0.8, 4.1)	0.004*

ADCS-Instrumental ADL - Alzheimer's disease cooperative study-Instrumental activities of daily living subscale
ANCOVA - analysis of covariance CI - confidence interval DLSM - difference in lease square means

ADCS-Instrumental ADL scores are caregiver-based, and range from 0 to 56, with higher scores indicating less severe impairment. A positive difference in DLSM indicates greater improvement in Exelon 15 cm² as compared to Exelon 10 cm².

n is the number of patients with an assessment at baseline (last assessment in the initial open-label phase) and either the corresponding visit (for the OC) or with at least 1 post baseline assessment (for the LOCF).

The DLSM, 95% CI, and p-value are based on an ANCOVA model adjusted for country and baseline ADCS-Instrumental ADL score.

As demonstrated in the preceding graphics, the difference in the change from Baseline scores on the ADCS-IADL in the DB-ITT LOCF population between treatment groups was statistically

significant at Week 48 which was the study's pre-defined co-primary outcome measure. Similar statistically significant differences in the change from Baseline in ADCS-IADL scores between treatment groups were also evident at Weeks 16, 24, and 32 in both the DB-ITT LOCF and OC populations.

Despite the expected similar amount of missing data in the analysis of the ADCS-IADL scores, relative to the ADAS-cog scores, the difference between groups remained significant at the Week 48 timepoint.

5.3.1.13.4.1.3 Supportive Analyses

The sponsor has also conducted several additional supportive analyses with respect to the trial's co-primary endpoints.

For both co-primary variables, an analysis of the DB-ITT LOCF population was conducted using the non-parametric van Elteren test stratified by country.

Sensitivity analyses were performed on the DB-ITT OC population for both co-primary variables using a mixed-effects repeated-measures model (MMRM) that examined the treatment group differences as a function of time. This model included fixed effects for treatment group, country, baseline score, visit, and treatment group-by-visit interaction and random effect for subject nested within treatment group.

Additional sensitivity analyses were performed to evaluate the possibility that missing primary efficacy measure data may not be missing at random utilizing multiple imputations under missing-at-random (MAR) and missing-not-at-random (MNAR) scenarios using penalty scores. The penalties were specified assuming a more pronounced progression of the disease after study discontinuation for the subjects who discontinued from the study as compared to those who remained in the study.

The sponsor suggests that the results of these sensitivity analyses (which have been provided in tabular form in the CSR) indicate that the conclusions from the primary analysis proved to be robust against different assumptions with respect to the missing values mechanism. A detailed review of these analyses is deferred to the Biometrics reviewer for this submission.

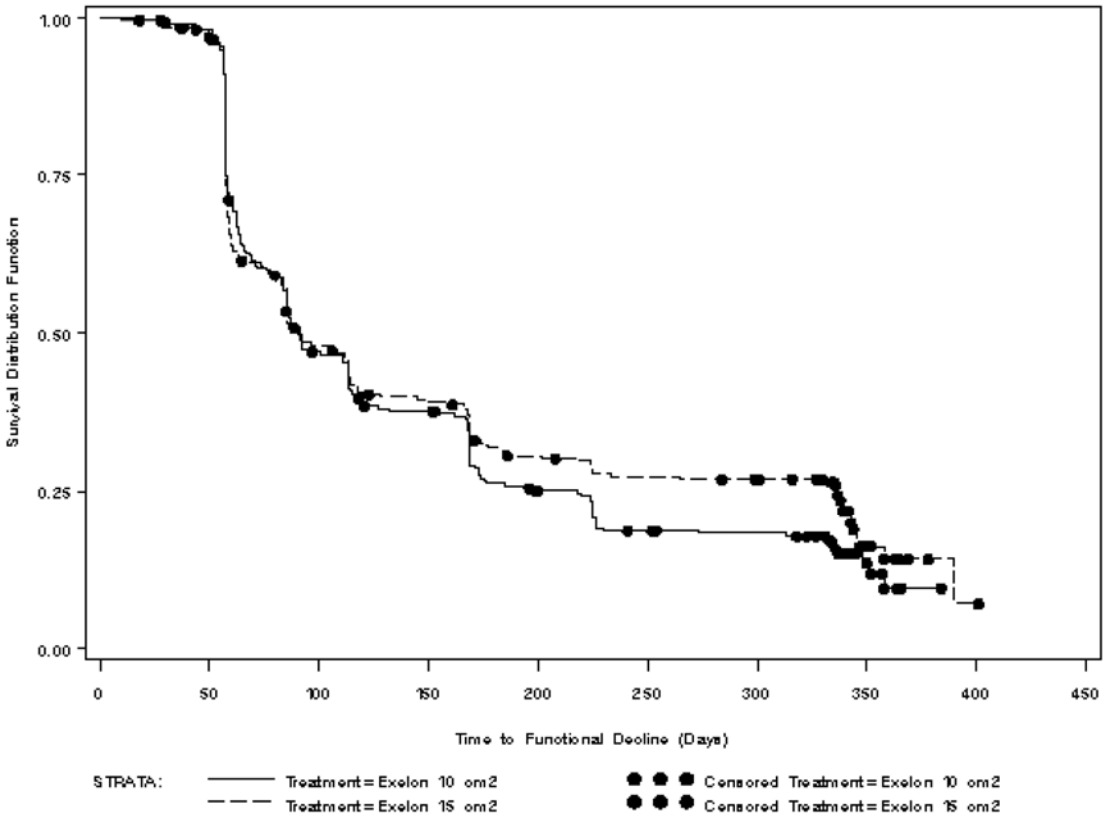
5.3.1.13.4.2 Secondary Efficacy Results

5.3.1.13.4.2.1 Time to Functional Decline as Measured by ADCS-IADL in the DB Phase

In the trial's DB phase, functional decline was defined by the sponsor as either an at least 1 point decrease in the ADCS-IADL score in a visit and confirmed at the following visit or at least a 2 point decrease from DB randomization baseline, and still at least 1 point less at the subsequent confirmation visit. This analysis was carried out for the DB-ITT and DB-PP population with OC.

The following graphic, copied from the submission, illustrates the time to functional decline in ADCS-IADL scores in the DB phase by treatment group in the DB-ITT OC population:

Figure 11-5 Time to functional decline in ADCS-Instrumental ADL in the DB phase, by treatment group (ITT-DB population, OC)



Time is calculated from date of randomization.

The differences between treatment groups based on the p-value of the log-rank test was not significant (p=0.186). Similar results were seen with the DB-PP OC dataset (p=0.061).

5.3.1.13.4.2.2 Trail Making Test (Parts A and B) in the DB Phase

The following table, copied from the submission, illustrates the change from baseline in Trail Making Test (Parts A and B) in the DB phase by treatment group (DB-ITT population):

Table 11-8 Change from baseline in Trail Making Test (TMT) Part A and B in the double-blind phase, by treatment group and visit (ITT-DB population)

Population / Visit		Exelon 15 cm^2		Exelon 10 cm^2		Exelon 15 cm^2 - Exelon 10 cm^2		
		n	Mean	n	Mean	DLSM	95% CI	p-value
Trail making test (TMT) - Part A								
LOCF	Baseline	254	191.3	258	199.4			
Week 24	Post-baseline	254	195.6	258	209.6			
	Change	254	4.2	258	10.2	-7.8	(-17.3, 1.7)	0.105
Week 48	Post-baseline	254	207.6	258	217.6			
	Change	254	16.3	258	18.2	-3.8	(-14.3, 6.6)	0.473
OC	Baseline	214	177.2	204	186.2			
Week 24	Post-baseline	214	182.3	204	199.1			
	Change	214	5.0	204	12.9	-10.6	(-22.1, 1.0)	0.072
Week 48	Baseline	163	172.4	142	169.2			
	Post-baseline	163	195.0	142	192.8			
	Change	163	22.6	142	23.5	-0.9	(-15.9, 14.1)	0.905
Trail making test (TMT) - Part B								
LOCF	Baseline	235	372.2	236	380.8			
Week 24	Post-baseline	235	377.7	236	381.6			
	Change	235	5.5	236	0.9	1.6	(-9.9, 13.1)	0.784
Week 48	Post-baseline	235	381.4	236	386.6			
	Change	235	9.3	236	5.8	0.8	(-10.1, 11.8)	0.881
OC	Baseline	189	364.7	178	370.9			
Week 24	Post-baseline	189	371.5	178	372.1			
	Change	189	6.9	178	1.2	2.8	(-11.8, 17.5)	0.704
Week 48	Baseline	139	360.9	120	366.2			
	Post-baseline	139	370.5	120	371.0			
	Change	139	9.6	120	4.8	1.7	(-15.6, 18.9)	0.850

The baseline assessment corresponds to the last assessment in the initial open-label (IOL) phase.

A negative change indicates an improvement from baseline. A negative difference (DLSM) indicates greater improvement in Exelon 15cm^2 as compared to Exelon 10cm^2.

Difference of least square means (DLSM), 95% confidence interval (CI), and p-value are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline TMT score.

* $p < 0.05$

n is the number of patients with an assessment at baseline and the corresponding visit (OC) and at least 1 post-baseline assessment (LOCF).

As is evident from the table, none of the differences between treatment groups are statistically significant.

5.3.1.13.4.2.3 Neuropsychiatric Inventory (NPI) in the DB Phase

The following table, copied from the submission, summarizes the change from baseline in NPI scores by treatment group in the DB-ITT population:

Table 11-9 Change from baseline in Neuropsychiatric Inventory (NPI) score, by treatment group (ITT-DB population)

Population		Exelon 15 cm^2		Exelon 10 cm^2		Exelon 15 cm^2 - Exelon 10 cm^2		
Visit		n	Mean	n	Mean	DLSM	95% CI	p-value
Neuropsychiatric Inventory (NPI) 10 - Total Score								
LOCF	Baseline	265	12.4	271	14.4			
DB endpoint	Post-baseline	265	13.8	271	15.4			
	Change	265	1.4	271	0.9	-0.1	(-1.9, 1.7)	0.927
OC	Baseline	243	11.8	241	13.7			
DB endpoint	Post-baseline	243	13.3	241	14.7			
	Change	243	1.5	241	1.1	-0.1	(-2.1, 1.9)	0.899
NPI-D: Distress score								
LOCF	Baseline	265	6.5	271	8.1			
endpoint	Post-baseline	265	7.1	271	8.1			
	Change	265	0.6	271	-0.0	0.2	(-0.7, 1.2)	0.647
OC	Baseline	243	6.1	241	7.7			
DB endpoint	Post-baseline	243	6.8	241	7.7			
	Change	243	0.7	241	-0.0	0.2	(-0.8, 1.2)	0.707

DB-endpoint is the last assessment during double-blind phase.

A negative change indicates an improvement from baseline. A negative difference (DLSM) indicates greater improvement in Exelon 15cm^2 as compared to Exelon 10cm^2.

Difference of least square means (DLSM), 95% confidence interval (CI), and p-value are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline NPI score.

* $p < 0.05$

n is the number of patients with an assessment at baseline and DB-endpoint.

As is evident from the table, there were no differences between treatment groups.

5.3.1.13.4.3 Exploratory Efficacy Results

The sponsor has also conducted a series of exploratory analyses on the data from both the trial's IOL phase as well as the EOL Phase. The results of these analyses are non-contributory to the overall interpretation of the trial's key findings and are therefore not discussed in this review.

5.3.1.13.5 Safety Results

5.3.1.13.5.1 Exposure

The following tables, copied from the submission, summarize the exposure to study medication in the Safety-IOL, Safety-DB, and Safety-EOL populations respectively:

Table 12-3 Duration of exposure to study medication for the IOL phase by study period and decline status (Safety-IOL population)

Duration of exposure (weeks)	Decliners N = 567	Non-decliners N = 459	Discontinued N = 556	Total N = 1582
Exposure - n (%)				
Any exposure in IOL phase	567 (100.0)	459 (100.0)	556 (100.0)	1582 (100.0)
≤ IOL Week 4	0 (0.0)	0 (0.0)	59 (10.6)	59 (3.7)
> IOL Week 4 to ≤ IOL Week 8	0 (0.0)	0 (0.0)	73 (13.1)	73 (4.6)
> IOL Week 4 to ≤ IOL Week 12	0 (0.0)	0 (0.0)	73 (13.1)	73 (4.6)
> IOL Week 12 to ≤ IOL Week 16	2 (0.4)	0 (0.0)	45 (8.1)	47 (3.0)
> IOL Week 16 to ≤ IOL Week 24	109 (19.2)	0 (0.0)	70 (12.6)	179 (11.3)
> IOL Week 24 to ≤ IOL Week 32	101 (17.8)	1 (0.2)	65 (11.7)	167 (10.6)
> IOL Week 32 to ≤ IOL Week 36	78 (13.8)	0 (0.0)	23 (4.1)	101 (6.4)
> IOL Week 36 to ≤ IOL Week 48	178 (31.4)	254 (55.3)	101 (18.2)	533 (33.7)
> IOL Week 48	99 (17.5)	204 (44.4)	47 (8.5)	350 (22.1)
Summary statistics (weeks)				
n	567	459	556	1582
Mean (SD)	36.40 (10.507)	48.50 (1.874)	22.84 (16.450)	35.15 (15.530)
Median	36.00	48.00	19.00	40.35
Range	15.4 - 59.0	25.9 - 61.1	0.1 - 58.7	0.1 - 61.1

A patient is counted in only 1 duration range, such that the total duration of exposure for that patient is within the range of that category.

As would be expected, the mean exposure in the IOL phase was shorter in decliners (36.40 weeks) when compared to non-decliners (48.50 weeks) as decliners could be randomized to the DB phase as early as Week 24 while non-decliners remained in the IOL phase through Week 48.

Table 12-4 Duration of exposure to study medication in the double-blind phase by study period and treatment group (Safety-DB population)

Duration of Exposure (weeks)	Exelon 15 cm^2 N = 280	Exelon 10 cm^2 N = 283	Total N = 563
Exposure-n (%)			
Any exposure in the double-blind phase	280 (100.0)	283 (100.0)	563 (100.0)
≤ DB to 4 Weeks	5 (1.8)	4 (1.4)	9 (1.6)
> DB-Week 4 to ≤ DB-Week 8	9 (3.2)	11 (3.9)	20 (3.6)
> DB-Week 8 to ≤ DB-Week 12	11 (3.9)	7 (2.5)	18 (3.2)
> DB-Week 12 to ≤ DB-Week 16	10 (3.6)	5 (1.8)	15 (2.7)
> DB-Week 16 to ≤ DB-Week 24	11 (3.9)	15 (5.3)	26 (4.6)
> DB-Week 24 to ≤ DB-Week 32	7 (2.5)	19 (6.7)	26 (4.6)
> DB-Week 32 to ≤ DB-Week 36	8 (2.9)	5 (1.8)	13 (2.3)
> DB-Week 36 to ≤ DB-Week 48	118 (42.1)	120 (42.4)	238 (42.3)
> DB-Week 48	101 (36.1)	97 (34.3)	198 (35.2)
Duration of exposure (weeks)			
n	280	283	563
Mean (SD)	41.39 (14.309)	41.28 (13.604)	41.33 (13.947)
Median	48.00	48.00	48.00
Range	1.3 - 57.1	1.3 - 56.1	1.3 - 57.1

A patient is counted in only 1 duration range, such that the total duration of exposure for that patient is within the range of that category.

Both treatment groups were similar with respect to the mean and median duration of exposure in the DB treatment phase of the trial.

Table 12-5 Duration of exposure to study medication for the extended open-label phase, by study period (Safety-EOL population)

Duration of exposure (weeks)		Total N = 457
Exposure - n (%)	Any exposure in EOL phase	457 (100.0)
	≤ EOL Week 4	5 (1.1)
	> EOL Week 4 to ≤ EOL Week 8	4 (0.9)
	> EOL Week 4 to ≤ EOL Week 12	9 (2.0)
	> EOL Week 12 to ≤ EOL Week 16	5 (1.1)
	> EOL Week 16 to ≤ EOL Week 24	13 (2.8)
	> EOL Week 24 to ≤ EOL Week 32	7 (1.5)
	> EOL Week 32 to ≤ EOL Week 36	3 (0.7)
	> EOL Week 36 to ≤ EOL Week 48	212 (46.4)
	> EOL Week 48	199 (43.5)
Summary statistics (weeks)	n	457
	Mean (SD)	45.36 (10.343)
	Median	48.00
	Range	0.6 - 63.0

A patient is counted in only 1 duration range, such that the total duration of exposure for that patient is within the range of that category.

As is apparent from the preceding table, the majority of subjects who successfully entered the EOL portion of the trial remained on treatment for > 36 weeks.

5.3.1.13.5.2 Concomitant Medications

With respect to the use of concomitant medication during the study, the sponsor notes that in each of the overall populations in the respective treatment phases, the vast majority of patients (97%) were treated with concomitant medications or therapies. Consistently the most commonly used concomitant medications were salicylic acid and derivatives (e.g. acetylsalicylic acid), and HMG coA reductase inhibitors (statins).

The following table, copied from the submission, summarizes the newly introduced pre-specified CNS medications during the trial's DB phase by treatment group:

Table 12-6 Newly introduced pre-specified CNS-related concomitant medications during the double- blind phase, by CNS drug group, preferred term, and treatment group (Safety-DB population)

Medication type	Exelon 15 cm^2 N = 280	Exelon 10 cm^2 N = 283	Total N = 563
Newly introduced CNS related medication			
Any CNS group	59 (21.1)	57 (20.1)	116 (20.6)
Antidepressant	28 (10.0)	24 (8.5)	52 (9.2)
Antipsychotic	25 (8.9)	28 (9.9)	53 (9.4)
Hypnotic/anxiolytic	17 (6.1)	18 (6.4)	35 (6.2)
Discontinued CNS related medication			
Any CNS group	19 (6.8)	20 (7.1)	39 (6.9)
Antidepressant	6 (2.1)	7 (2.5)	13 (2.3)
Antipsychotic	6 (2.1)	10 (3.5)	16 (2.8)
Hypnotic/anxiolytic	7 (2.5)	8 (2.8)	15 (2.7)

The percentages of subjects receiving each class of medication were similar between the treatment groups.

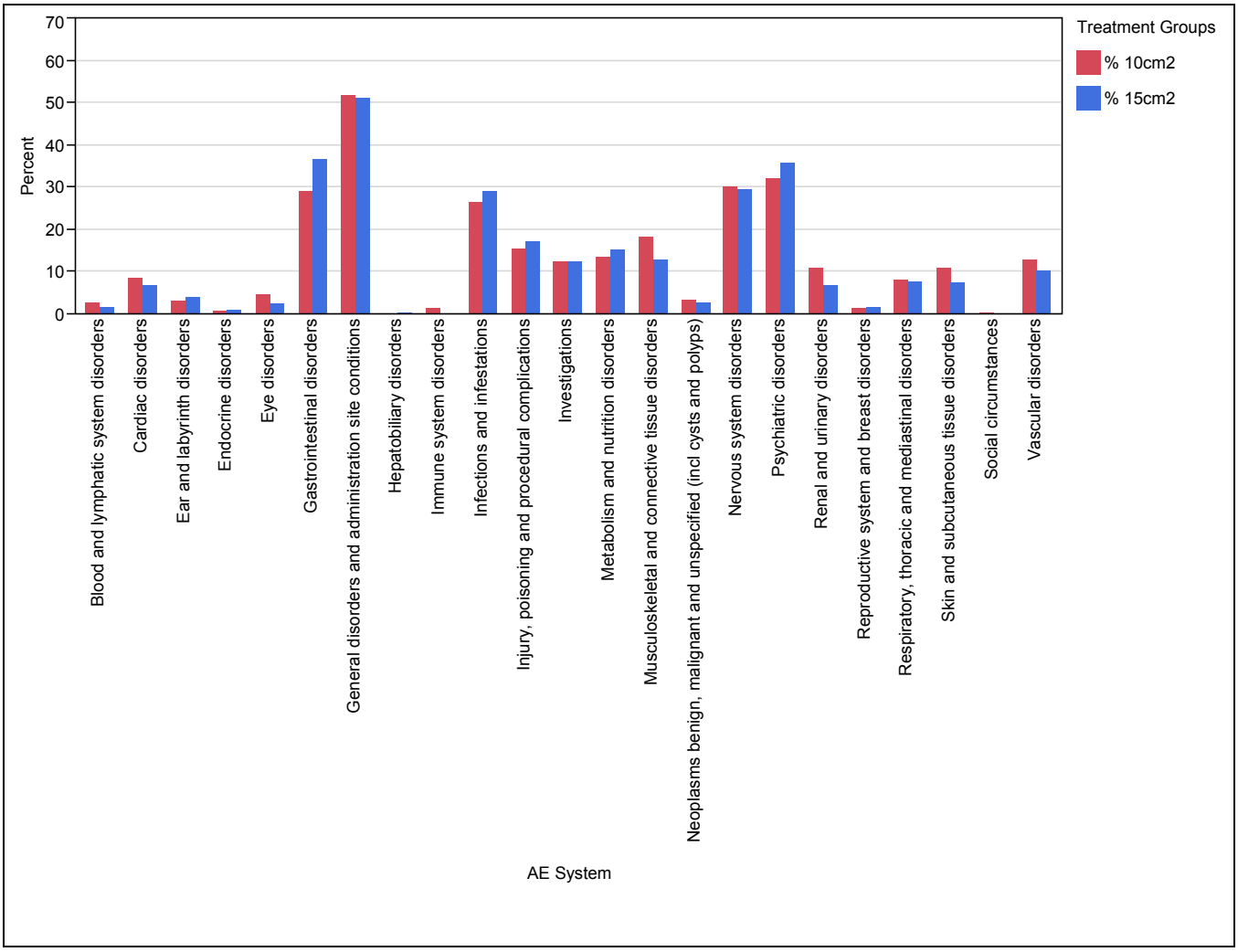
5.3.1.13.5.3 Adverse Events

The submission has provided AE data for both the IOL and EOL phases of the trial. However, as the focus of this review is the approvability of the 15cm^2 dose of the Exelon® Patch, the AE analysis will be largely restricted to the DB phase of the trial.

5.3.1.13.5.3.1 Common Adverse Events

The following graph and accompanying table, respectively, sumarize the adverse events that were observed in the DB phase of the trial by System Order Class (SOC) and treatment group:

Adverse Events by System Order Class by Treatment Group (Safety-DB Population)



Adverse Events by System Order Class by Treatment Group (Safety-DB Population)

	Exelon 10 cm2 N=283		Exelon 15 cm2 N=280	
Adverse Event Class	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders	8	2.83	5	1.79
Cardiac disorders	24	8.48	19	6.79
Ear and labyrinth disorders	9	3.18	11	3.93
Endocrine disorders	2	0.71	3	1.07
Eye disorders	13	4.59	7	2.50
Gastrointestinal disorders	82	28.98	102	36.43
General disorders and administration site conditions	146	51.59	143	51.07
Hepatobiliary disorders	0	0.00	1	0.36
Immune system disorders	4	1.41	0	0.00
Infections and infestations	75	26.50	81	28.93
Injury, poisoning and procedural complications	44	15.55	48	17.14
Investigations	35	12.37	35	12.50
Metabolism and nutrition disorders	38	13.43	43	15.36
Musculoskeletal and connective tissue disorders	52	18.37	36	12.86
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10	3.53	8	2.86
Nervous system disorders	85	30.04	82	29.29
Psychiatric disorders	91	32.16	100	35.71
Renal and urinary disorders	31	10.95	19	6.79
Reproductive system and breast disorders	4	1.41	5	1.79
Respiratory, thoracic and mediastinal disorders	23	8.13	22	7.86
Skin and subcutaneous tissue disorders	31	10.95	21	7.50
Social circumstances	1	0.35	0	0.00
Vascular disorders	36	12.72	28	10.00

While the overall incidence of AEs was generally comparable between arms, the occurrence of gastrointestinal disorders was somewhat higher in the 15cm^2 group [36.43 versus 28.98% (+ 7.45%)].

The table below further describes the occurrence of the common adverse events that were observed in the DB phase of the trial. The cutoff of >3% was selected in that the likelihood of a rare but serious AE is extremely improbable in the setting of a modestly higher dose of this already approved drug with a substantial amount of existing safety data. Additionally, the analysis of SAEs would also be able to detect any unforeseen rare events.

Common Adverse Events (>3% in Either Treatment Group) by Treatment Group (Safety-DB Population)

	Exelon 10 cm2 N=283		Exelon 15 cm2 N=280	
Adverse Event (Preferred Term)	**N**	**%**	**N**	**%**
Abdominal pain (all)	11	3.88	21	7.50

	Exelon 10 cm2 N=283		Exelon 15 cm2 N=280	
Adverse Event (Preferred Term)	**N**	**%**	**N**	**%**
Aggression	13	4.59	9	3.21
Agitation	21	7.42	21	7.50
Anxiety	11	3.89	22	7.86
Application site erythema	37	13.07	45	16.07
Application site irritation	10	3.53	10	3.57
Application site pruritus	25	8.83	30	10.71
Application site rash	10	3.53	12	4.29
Confusional state	10	3.53	11	3.93
Constipation	6	2.12	9	3.21
Cough	7	2.47	9	3.21
Decreased appetite	12	4.24	22	7.86
Delusion	9	3.18	8	2.86
Depression	26	9.19	23	8.21
Diarrhea	25	8.83	25	8.93
Dizziness	9	3.18	16	5.71
Fall	27	9.54	25	8.93
Fatigue	8	2.83	11	3.93
Headache	18	6.36	17	6.07
Hypertension	19	6.71	16	5.71
Insomnia	11	3.89	19	6.79
Nasopharyngitis	9	3.18	15	5.36
Nausea	19	6.71	42	15.00
Edema peripheral	11	3.89	10	3.57
Psychomotor hyperactivity	16	5.65	11	3.93
Syncope	7	2.47	12	4.29
Urinary incontinence	13	4.59	12	4.29
Urinary tract infection	17	6.01	25	8.93
Vomiting	22	7.77	36	12.86
Weight decreased	18	6.36	25	8.93

Note: The verbatim terms used for the MeDRA coding by the sponsor were reviewed and compared to the selected preferred terms. In general, the selected preferred terms accurately reflect the reported verbatim terms.

As the highlighted rows in the preceding table demonstrate, the rates of several GI-related AEs were more common in the 15cm^2 group. In particular, vomiting was observed in 12.86 versus 7.77% (+ 5.09%) of subjects in the 15cm^2 arm as compared to the 10cm^2 arm. Nausea was also observed in 15.00 versus 6.71% (+ 5.09%) of subjects in the 15cm^2 arm as compared to the 10cm^2 arm. The rate of diarrhea was essentially identical between the groups at approximately 9% in each. Also of note, insomnia, which is an established AE in association with the use of cholinesterase inhibitors, was also almost twice as common in the 15cm^2 arm (6.70 versus 3.89%).

Although the strength of this observation is limited by the nature of the intra-study comparison, it should be pointed out that the respective rates of nausea and vomiting observed for the 15cm^2 Exelon® Patch are lower than what was observed in the pivotal studies used for the approval of the Exelon® oral formulations (both tablet and solution) where the rate of nausea was 47% and the rate of vomiting was 31% in Alzheimer's disease patients. The rates for nausea and vomiting in the trial in Parkinson's disease patients were 29 and 17%, respectively.

The following table, created from information provided in the submission, summarizes the severity of the reported AEs of interest (overall and for selected AEs of interest) in the Safety-DB population:

Primary SOC	Preferred Term	Maximum Severity	Exelon 15cm^2 N=280 n (%)	Exelon 10cm^2 N=283 n (%)	Total N=563 n (%)
Cardiac Disorders	Total	Mild	6 (2.1)	7 (2.5)	13 (2.3)
		Moderate	3 (1.1)	7 (2.5)	10 (1.8)
		Severe	3 (1.1)	5 (1.8)	8 (1.4)
Gastrointestinal Disorders	Total	Mild	45 (16.1)	27 (9.5)	72 (12.8)
		Moderate	32 (11.4)	21 (7.4)	53 (9.4)
		Severe	5 (1.8)	6 (2.1)	11 (2.0)
	Nausea	Mild	18 (6.4)	6 (2.1)	24 (4.3)
		Moderate	15 (5.4)	6 (2.1)	21 (3.7)
		Severe	1 (0.4)	2 (0.7)	3 (0.5)
	Vomiting	Mild	12 (4.3)	5 (1.8)	17 (3.0)
		Moderate	12 (4.3)	5 (1.8)	17 (3.0)
		Severe	5 (1.8)	3 (1.1)	8 (1.4)
	Diarrhea	Mild	15 (5.4)	10 (3.5)	25 (4.4)
		Moderate	3 (1.1)	3 (1.1)	6 (1.1)
Investigations	Weight Decreased	Mild	13 (4.6)	4 (1.4)	17 (3.0)
		Moderate	5 (1.8)	4 (1.4)	9 (1.6)
		Severe	1 (0.4)	0 (0.0)	1 (0.2)
Nervous System Disorders	Total	Mild	24 (8.6)	20 (7.1)	44 (7.8)
		Moderate	28 (10.0)	26 (9.2)	54 (9.6)
		Severe	8 (2.9)	6 (2.1)	14 (2.5)
Psychiatric Disorders	Total	Mild	26 (9.3)	22 (7.8)	48 (8.5)
		Moderate	39 (13.9)	33 (11.7)	72 (12.8)
		Severe	6 (2.1)	6 (2.1)	12 (2.1)

As the preceding table indicates, the majority of AEs were rated mild to moderate in both treatment arms. Patients in the 15cm^2 dose group had somewhat higher rates of mild to moderate nausea and vomiting when compared to the 10cm^2 dose group, however, rates of severe nausea/vomiting were low and comparable between the groups.

5.3.1.13.5.3.2 Deaths, other Serious Adverse Events, and Discontinuations due to Adverse Events

The number and proportion of patients in each treatment group who died, experienced serious adverse events (SAEs), or discontinued due to adverse events (AEs) during the DB phase of the trial is summarized in the following table which is copied from the submission:

Event	Exelon 15 cm^2 N = 280 n (%)	Exelon 10 cm^2 N = 283 n (%)	Total N = 563 n (%)
Death	3 (1.1)	5 (1.8)	8 (1.4)
Serious adverse events (SAEs) [(a)]	44 (15.7)	44 (15.5)	88 (15.6)
Discontinued due to adverse events (AEs) [(a)]	27 (9.6)	36 (12.7)	63 (11.2)
Discontinued due to SAE (s) [(a)]	12 (4.3)	18 (6.4)	30 (5.3)

(a) Deaths are included.

As with other analyses conducted in this review, this assessment will be largely confined to the DB phase of the trial as the principle question at hand is the evaluation of the 15cm^2 Exelon® Patch. The preceding table indicates that the percentage of subjects who discontinued their participation in the trial due to both AEs and SAEs was higher in the 10cm^2 treatment arm (12.7 versus 9.6% for AEs and 6.4 versus 4.3% for SAEs).

5.3.1.13.5.3.2.1 Deaths

The following table, copied from the submission, provides an overview of the patients who died during any treatment phase of the trial:

Study phase and treatment group Patient Identification	Age/gender/race	Last dose study day	Death study day	Principal cause of death preferred term
Double-blind treatment phase - Exelon 15 cm^2				
0107/00006	83 year old Caucasian male	Day 542	Day 543	Cerebrovascular accident
0410/00005	80 year old Caucasian female	Day 424	Day 425	Cerebellar hemorrhage
0555/00001	61 year old Caucasian male	Day 228	Day 228	Pneumonia aspiration
Double-blind treatment phase - Exelon 10 cm^2				
0108/00001	82 year old Caucasian female	Day 535	Day 535	Colon cancer
0116/00007	77 year old Caucasian female	Day 295	Day 334	Colon cancer
0313/00004	75 year old Caucasian female	Day 240	Day 242	Pneumonia
0423/00004	75 year old Caucasian male	Day 346	Day 351	Acute respiratory distress syndrome
0567/00019	84 year old Caucasian male	Day 349	Day 351	Renal failure
Initial open-label treatment phase - Exelon 10 cm^2				
0115/00010	79 year old Caucasian male	Day 176	Day 179	Neurological decompensation.
0623/00009	81 year old Caucasian male	Day 176	Day 179	Cardiac failure
0302/00004	80 year old Caucasian female	Day 309	Day 309	Dementia Alzheimer's type
0307/00007	76 year old Caucasian male	Day 327	Day 335	Bronchial carcinoma
0328/00011	69 year old Caucasian male	Day 72	Day 76	Myocardial infarction
0203/00008	84 year old Caucasian male	Day 71	Day 81	Coma
0205/00014	82 year old Caucasian female	Day 200	Day 205	Femoral neck fracture
0207/00016	77 year old Caucasian male	Day 33	Day 33	Aortic rupture
0401/00005	72 year old Caucasian male	Day 122	Day 141	Acute myeloid leukemia
0414/00007	75 year old Caucasian female	Day 103	Day 103	Myocardial infarction
0427/00006	77 year old Caucasian male	Day 1	Day 1	Injury (1)
0502/00011	81 year old Caucasian female	Day 252	Day 268	Dementia Alzheimer's type
0503/00009	81 year old Caucasian male	Day 158	Day 159	Myocardial infarction
0512/00005	78 year old Caucasian male	Day 37	Day 37	Injury (1)
0515/00009	80 year old Caucasian female	Day 106	Day 119	Cardio-respiratory arrest
0527/00004 (2)	82 year old Caucasian male	None	Day 13	Respiratory failure
0527/00010	82 year old Caucasian female	Day 177	Day 181	Cryptogenic cirrhosis
0527/00031	74 year old Caucasian male	Day 128	Day 137	Embolic cerebral infarction
0543/00001	79 year old Caucasian female	Day 13	Day 16	Neurological symptom
0549/00008	80 year old Caucasian male	Day 52	Day 55	Traumatic fracture
0566/00012	84 year old Caucasian female	Day 38	Day 39	Coronary artery disease
0567/00006	77 year old Caucasian female	Day 169	Day 170	Hepatic neoplasm malignant
Extended open-label treatment phase - Exelon 10 cm^2				
0110/00003	75 year old Caucasian male	Day 398	Day 399	Hip fracture
0117/00007	76 year old Caucasian male	Day 639	Day 639	Colon neoplasm
0303/00009	83 year old Caucasian male	Day 638	Day 638	Central nervous system lesion
0321/00009	84 year old Caucasian female	Day 506	Day 506	Pneumonia aspiration
0322/00005	70 year old Caucasian male	Day 351	Day 352	Cardiac arrest
0539/00007	70 year old Caucasian female	Day 553	Day 560	Dementia Alzheimer's type
0567/00028	75 year old Caucasian female	Day 518	Day 518	Cerebral hemorrhage

Day is relative to the first day of treatment during the initial open-label phase (Day 1).

(1) Injuries sustained in a motor vehicle accident.
(2) This patient did not receive study drug during the 13 days in the study (PT-Listing 16.2.9-1.7).

I have read the narratives for the deaths listed in the preceding table.

On first inspection, subject **0555/00001** was potentially of concern in that the patient was relatively young at age 61 and died suddenly of aspiration pneumonia. The subject had a largely non-contributory medical history at enrollment (July 16, 2007) and had been diagnosed with AD in April 2006. He had previously been prescribed memantine hydrochloride and had also been taking donepezil (started in December 2006) which was discontinued prior to receiving study medication. The subject's MMSE score decline precipitously during the IOL phase of the trial from a Baseline score of 14 on August 1, 2007 to a score of 0 at the last reported visit in the IOL phase on January 17, 2008. Due to the subject's meeting the criteria as a decliner in the IOL phase, he was randomized to receive the 15cm^2 patch on January 18, 2008 in the DB phase. Notably, the subject developed an infected sacral ulcer requiring hospitalization in (b) (6) which subsequently resolved. The subject was also treated for a UTI, worsening pericarditis, and *Candida* induced diarrhea in October 2007, all of which apparently responded to therapy. Most relevant to the current application is the fact that on March 6, 2008 the subject was noted to have about a 7 pound weight loss in one week's time and also developed mild dehydration, increased pulse rate, and a decreased oxygen saturation level. On March 7, 2008 the subject was diagnosed with a severe aspiration pneumonia and subsequently died on (b) (6) despite treatment with antibiotics and oxygen.

It is concerning in its own right that this subject, who declined 14 points on the MMSE to a score of 0 during only a 5 month period during the IOL phase, was deemed appropriate for randomization into the DB phase. While this decline could be contributed to a series of medical comorbidities and their sequelae, the ability of any subject with a MMSE score of 0 to provide interpretable information on the assessment tools used in the current trial is highly suspect. The cause of death is also potentially of concern in that aspiration pneumonia could conceivably be attributed to gastrointestinal symptoms related to a higher dose of study medication. That said, the fact that this is a single occurrence in a subject who had a substantially compromised medical state and had also been on the higher patch dose for 2 months prior to death, makes any relative contribution of the higher dose patch difficult to ascertain and questionable at best. Aspiration pneumonia is also widely reported as a leading cause of death in AD patients irrespective of treatment.

All of the other deaths that occurred in this trial appear to be due to incidental illnesses that are common in the elderly; none is easily attributable to study drug.

5.3.1.13.5.3.2.2 Serious Adverse Events

The following table outlines the serious adverse events observed in the DB phase of the trial organized by High Level Group Term (HLGT):

Serious Adverse Events (SAEs) by High Level Group Term (HGLT) by Treatment Group (Safety-DB Population)

	Exelon 10 cm2 N=283		Exelon 15 cm2 N=280	
High Level Group Term (HLGT)	**N**	**%**	**N**	**%**

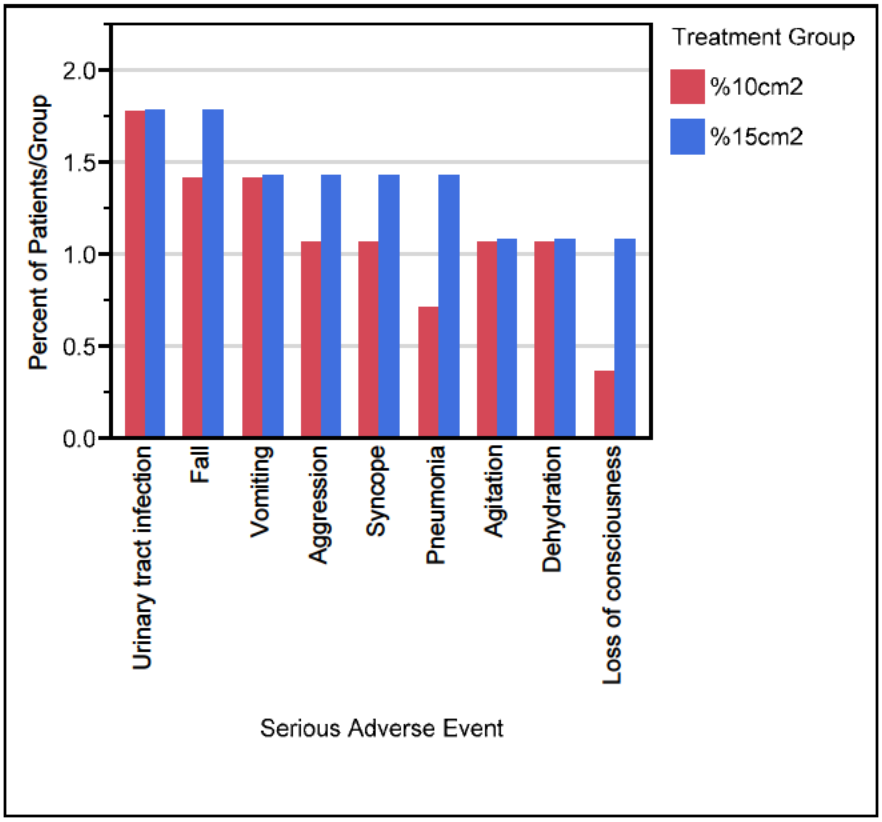
	Exelon 10 cm2 N=283		Exelon 15 cm2 N=280	
High Level Group Term (HLGT)	**N**	**%**	**N**	**%**
Abdominal hernias and other abdominal wall conditions	1	0.35	1	0.36
Administration site reactions	1	0.35	0	0.00
Adrenal gland disorders	0	0.00	1	0.36
Anxiety disorders and symptoms	4	1.41	4	1.43
Appetite and general nutritional disorders	0	0.00	4	1.43
Arteriosclerosis, stenosis, vascular insufficiency and necrosis	1	0.35	0	0.00
Bacterial infectious disorders	0	0.00	1	0.36
Benign neoplasms gastrointestinal	1	0.35	0	0.00
Body temperature conditions	1	0.35	1	0.36
Bone and joint injuries	7	2.47	10	3.57
Breast neoplasms malignant and unspecified (incl nipple)	1	0.35	0	0.00
Cardiac arrhythmias	8	2.83	5	1.79
Central nervous system vascular disorders	3	1.06	4	1.43
Complications associated with device	1	0.35	0	0.00
Coronary artery disorders	5	1.77	1	0.36
Decreased and nonspecific blood pressure disorders and shock	1	0.35	2	0.71
Deliria (incl confusion)	3	1.06	2	0.71
Electrolyte and fluid balance conditions	3	1.06	3	1.07
Embolism and thrombosis	1	0.35	1	0.36
Enzyme investigations NEC	1	0.35	0	0.00
Epidermal and dermal conditions	2	0.71	1	0.36
Exocrine pancreas conditions	0	0.00	1	0.36
Fractures	1	0.35	0	0.00
Gastrointestinal conditions NEC	1	0.35	0	0.00
Gastrointestinal haemorrhages NEC	1	0.35	0	0.00
Gastrointestinal motility and defaecation conditions	2	0.71	1	0.36
Gastrointestinal neoplasms malignant and unspecified	3	1.06	0	0.00
Gastrointestinal signs and symptoms	5	1.77	5	1.79
Gastrointestinal stenosis and obstruction	2	0.71	0	0.00
General system disorders NEC	1	0.35	2	0.71
Glucose metabolism disorders (incl diabetes mellitus)	3	1.06	2	0.71
Heart failures	3	1.06	0	0.00
Hepatobiliary neoplasms malignant and unspecified	0	0.00	1	0.36
Infections - pathogen unspecified	13	4.59	13	4.64
Injuries NEC	7	2.47	6	2.14
Joint disorders	1	0.35	0	0.00
Lower respiratory tract disorders (excl obstruction and infection)	2	0.71	1	0.36
Mental impairment disorders	3	1.06	1	0.36
Metastases	1	0.35	0	0.00
Movement disorders (incl parkinsonism)	2	0.71	1	0.36
Musculoskeletal and connective tissue disorders NEC	3	1.06	0	0.00
Neurological disorders NEC	4	1.41	10	3.57
Neuromuscular disorders	0	0.00	1	0.36
Personality disorders and disturbances in	3	1.06	4	1.43

	Exelon 10 cm2 N=283		Exelon 15 cm2 N=280	
High Level Group Term (HLGT)	**N**	**%**	**N**	**%**
behaviour				
Procedural related injuries and complications NEC	1	0.35	0	0.00
Psychiatric and behavioural symptoms NEC	0	0.00	1	0.36
Psychiatric disorders NEC	1	0.35	0	0.00
Pulmonary vascular disorders	1	0.35	0	0.00
Renal disorders (excl nephropathies)	2	0.71	1	0.36
Reproductive neoplasms male malignant and unspecified	0	0.00	1	0.36
Respiratory disorders NEC	1	0.35	1	0.36
Schizophrenia and other psychotic disorders	1	0.35	0	0.00
Seizures (incl subtypes)	2	0.71	0	0.00
Skin neoplasms malignant and unspecified	1	0.35	2	0.71
Soft tissue sarcomas	1	0.35	0	0.00
Spinal cord and nerve root disorders	1	0.35	0	0.00
Suicidal and self-injurious behaviors NEC	2	0.71	0	0.00
Synovial and bursal disorders	1	0.35	0	0.00
Urinary tract signs and symptoms	1	0.35	0	0.00
Vascular hypertensive disorders	1	0.35	0	0.00
Viral infectious disorders	2	0.71	0	0.00

As this table indicates, the overall incidence of SAEs was generally comparable between groups and consistent with what is typically observed in a trial of this duration in an AD patient population.

The following graph further visualizes the occurrence of the most common SAEs by treatment group in the DB phase of the trial:

Most Common Serious Adverse Events (SAEs) by Treatment Group (Safety-DB Population)



Again, these SAEs are largely comparable between groups and in the cases where a difference is noted, the overall number of patients affected is quite low.

5.3.1.13.5.3.2.3 Discontinuations due to Adverse Events

The following table outlines the occurrence of discontinuations due to AEs (preferred term) by treatment group in the DB phase of the trial:

Adverse Events Leading to Treatment Discontinuation (Safety-DB Population)

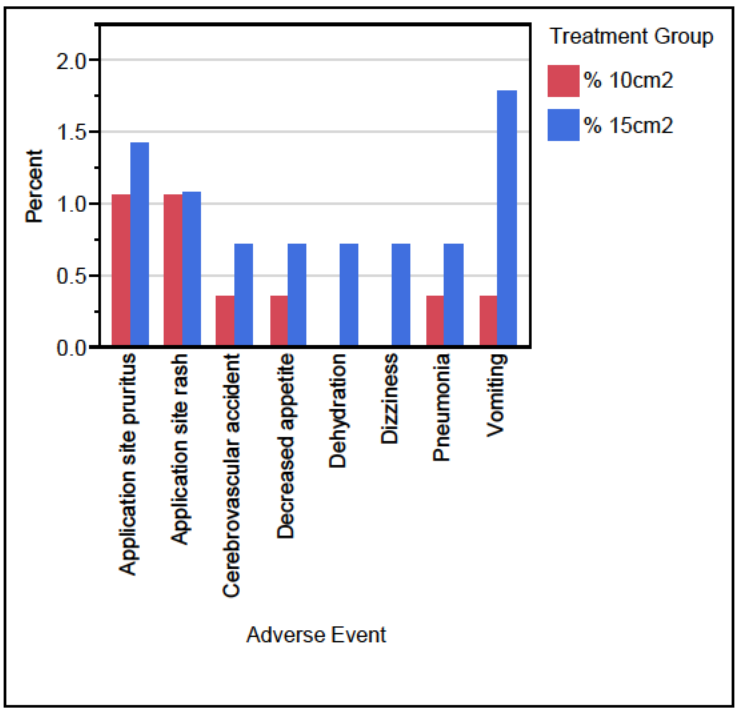
	Exelon 10 cm2 N=283		Exelon 15 cm2 N=280	
Adverse Event	**N**	**%**	**N**	**%**
Abdominal pain upper	1	0.35	0	0.00
Acute respiratory distress syndrome	1	0.35	0	0.00
Aerophagia	1	0.35	0	0.00
Aggression	3	1.06	1	0.36
Agitation	0	0.00	1	0.36
Akathisia	1	0.35	0	0.00
Application site erythema	3	1.06	0	0.00
Application site hypersensitivity	2	0.71	0	0.00
Application site irritation	0	0.00	1	0.36

	Exelon 10 cm2 N=283		Exelon 15 cm2 N=280	
Adverse Event	**N**	**%**	**N**	**%**
Application site pruritus	3	1.06	4	1.43
Application site rash	3	1.06	3	1.07
Application site swelling	1	0.35	0	0.00
Application site vesicles	1	0.35	0	0.00
Atrial fibrillation	2	0.71	0	0.00
Cardio-respiratory arrest	1	0.35	0	0.00
Cerebellar haemorrhage	0	0.00	1	0.36
Cerebral haemorrhage traumatic	1	0.35	0	0.00
Cerebrovascular accident	1	0.35	2	0.71
Colon cancer	2	0.71	0	0.00
Confusional state	1	0.35	1	0.36
Convulsion	1	0.35	0	0.00
Decreased appetite	1	0.35	2	0.71
Deep vein thrombosis	1	0.35	0	0.00
Dehydration	0	0.00	2	0.71
Delirium	2	0.71	1	0.36
Dementia	0	0.00	1	0.36
Dementia Alzheimer's type	0	0.00	1	0.36
Diarrhoea	1	0.35	0	0.00
Disinhibition	0	0.00	1	0.36
Disorientation	1	0.35	0	0.00
Dizziness	0	0.00	2	0.71
Drug eruption	1	0.35	0	0.00
Epilepsy	1	0.35	0	0.00
Failure to thrive	0	0.00	1	0.36
Fall	1	0.35	1	0.36
Fatigue	0	0.00	1	0.36
Hallucination, visual	1	0.35	0	0.00
Headache	0	0.00	1	0.36
Hepatic neoplasm malignant	0	0.00	1	0.36
Insomnia	1	0.35	0	0.00
Intestinal mass	1	0.35	0	0.00
Irritability	1	0.35	0	0.00
Leiomyosarcoma	1	0.35	0	0.00
Lip and/or oral cavity cancer	1	0.35	0	0.00
Loss of consciousness	1	0.35	0	0.00
Malnutrition	0	0.00	1	0.36
Nausea	1	0.35	1	0.36
Osteomyelitis	1	0.35	0	0.00
Pelvic fracture	1	0.35	0	0.00
Pneumonia	1	0.35	2	0.71
Pneumonia aspiration	0	0.00	1	0.36
Poor quality sleep	0	0.00	1	0.36
Psoriasis	1	0.35	0	0.00
Psychomotor hyperactivity	1	0.35	0	0.00
Rash generalised	0	0.00	1	0.36
Renal failure	1	0.35	0	0.00
Renal failure acute	1	0.35	0	0.00
Sepsis	1	0.35	0	0.00
Sinus arrhythmia	1	0.35	0	0.00
Syncope	1	0.35	0	0.00
Tachycardia	1	0.35	0	0.00
Tremor	0	0.00	1	0.36

	Exelon 10 cm2 N=283		Exelon 15 cm2 N=280	
Adverse Event	**N**	**%**	**N**	**%**
Vomiting	1	0.35	5	1.79
Weight decreased	0	0.00	1	0.36

The following graphic further helps to visualize the most common AEs leading to discontinuations in the DB phase of the trial:

Most Common AEs Leading to Discontinuation by Treatment Group (Safety-DB Population)



The most significant difference in these discontinuations relates to the occurrence of vomiting (1.79 versus 0.35% in the 15cm^2 and 10cm^2 groups, respectively). The overall numbers of subjects affected in these groups were only 5 and 1, however.

As was also pointed out previously, the percentage of patients who discontinued due to an AE in the DB phase of the trial was higher in the 10cm^2 treatment arm (12.7 versus 9.6%). Similarly, the overall number of patients who discontinued due to an SAE in the DB phase of the trial was also higher in the 10cm^2 treatment arm (6.4 versus 4.3%).

5.3.1.13.5.4 Vital Signs

The following table outlines the mean, minimum, and maximum values at Baseline and Week 48 for standing vital signs (systolic blood pressure, diastolic blood pressure, and pulse) by treatment group in the DB phase of the trial:

Standing Vital Signs by Treatment Group and Visit (Safety-DB Population)

		DBP			Pulse			SBP		
Treatment Arm	**Visit**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**
Exelon 10 cm^2	**BL**	76.3	48	121	73.2	51	103	131.7	84	176
	WK 48	75.0	45	108	73.0	48	108	128.2	90	182
Exelon 15 cm^2	**BL**	77.6	50	110	73.6	48	111	132.4	96	180
	WK 48	74.7	45	126	72.8	42	112	129.9	90	213

DBP=diastolic blood pressure
SBP=systolic blood pressure

The following table outlines the mean, minimum, and maximum values at Baseline and Week 48 for seated vital signs (systolic blood pressure, diastolic blood pressure, and pulse) by treatment group in the DB phase of the trial:

Seated Vital Signs by Treatment Group and Visit (Safety-DB Population)

		DBP			Pulse			SBP		
Treatment Arm	**Visit**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**	**Mean**	**Min**	**Max**
Exelon 10 cm^2	**BL**	75.0	49	100	69.9	52	100	131.8	90	179
	WK 48/PD	73.4	48	110	69.5	48	152	128.4	99	188
Exelon 15 cm^2	**BL**	75.4	49	114	70.4	47	101	132.5	96	180
	WK 48/PD	73.9	8	117	69.1	46	102	130.0	14	210

DBP=diastolic blood pressure
SBP=systolic blood pressure

There were no apparent meaningful differences between treatment groups in either standing or seated vital signs in the DB phase of the trial.

5.3.1.13.5.5 Body Weight

The following table summarizes the mean body weight by treatment group and study visit in the DB safety population:

Mean Weight by Treatment Group and Study Visit (Safety-DB Population)

Body Weight in Kg (Mean)		
Visit	**Exelon 10cm^2**	**Exelon 15cm^2**
SCR	67.8	69.4
BL	68.0	69.2
WK 4	67.8	69.5
WK 8	68.0	69.7
WK 12	67.9	69.5
WK 24	67.8	69.4
WK 36	68.0	69.4
WK 48	67.8	68.6

The mean body weight was slightly higher in the 15cm^2 group at all visits and there was no consistent trend toward weight loss in either treatment arm.

5.3.1.13.5.6 Electrocardiograms

The following table summarizes the mean electrocardiographic parameters at Baseline and Week 48 (of the DB phase) by treatment group in the Safety-DB population:

Mean ECG Parameters by Treatment Group and Visit (Safety-DB Population)

		PR Interval	QRS Duration	QTc	RR Interval	Ventricular Rate
Treatment Arm	**Visit**	**Mean**	**Mean**	**Mean**	**Mean**	**Mean**
Exelon 10 cm^2	**BL**	166.4	91.4	421.7	927.8	66.2
	WK 48	169.8	97.2	422.3	929.4	66.7
Exelon 15 cm^2	**BL**	181.1	102.0	420.9	978.0	62.9
	WK 48	170.2	97.7	420.1	953.0	65.6

Units are in milliseconds

There were no clinically significant findings with respect to any of these parameters and they were all considered to be in the normal range.

5.3.1.13.5.7 Other Safety Explorations

5.3.1.13.5.7.1 Time Dependency of Adverse Events

A direct comparison of the incidence of AEs between the two treatment arms in the DB portion of the study may be somewhat misleading in that subjects on the 10cm^2 dose had been receiving that treatment for at least 24 weeks in the IOL phase prior to the beginning of the DB phase. As a result, what is really being compared in this analysis is the rates of AEs in subjects who were already on a stable dose of the 10cm^2 patch versus subjects who were relatively recently titrated to the higher dose 15cm^2 dose.

Therefore, the table below which was created from data supplied in the submission, outlines the incidences of selected AEs of interest in the 15cm^2 dose group by whether they occurred in the first 4 weeks or after 24 weeks of the DB phase of the trial in the DB-Safety population. The table also presents the rates of select AEs of interest from the first 4 week of the DB phase of the trial from the 10cm^2 dose group

AE Preferred Term	Rate of AEs in DB Phase		
	15cm^2 Exelon Weeks 1-4 N=280 n (%)	15 cm^2 Exelon > 24 weeks N=241 n (%)	10cm^2 Exelon Weeks 1-4 N=283 n (%)
Nausea	18 (6.4)	10 (4.1)	3 (1.1)
Vomiting	14 (5.0)	6 (2.5)	2 (0.7)
Diarrhea	3 (1.1)	4 (1.7)	4 (1.4)
Dizziness	3 (1.1)	4 (1.7)	0 (0.0)
Fall	4 (1.4)	9 (3.7)	2 (0.7)

The preceding table now allows for the comparison of subjects who are already taking a stable dose of the 10cm^2 patch with subjects who have both been initially titrated to the higher dose 15cm^2 patch and those who have stabilized at that level. The table suggests that the rates of the selected AEs of interest either decline or remain infrequent in the 15cm^2 dose group over time, with the exception that subjects were more likely to experience a fall beyond 24 weeks. That said, it should be noted that the period beyond 24 weeks could last up to Week 48 while the initial period analyzed was confined to Weeks 1-4. For an AE like fall which would not be cumulative and also is known to be common in this population, the ratio of AE per week would be therefore similar.

While the rate of these selected AEs in the 15cm^2 following 24 weeks of exposure remains higher than the 10cm^2 group, the overall rate of these events is relatively low and the same caveat related to the different duration of exposures between these groups would also apply in this comparison.

5.3.1.13.5.7.2 Body Weight Dependency for Adverse Events

The following table outlines the incidence of selected adverse events of interest by body weight in the DB phase of the trial:

Adverse Events of Interest by Body Weight (Safety-DB Population)

Adverse Event	Weight		
	< 50kg N=27	50-80kg N=193	>80kg N=60
	n(%)	n(%)	n(%)
Diarrhea	3 (11.1)	17 (8.8)	5 (8.3)
Nausea	1 (3.7)	32 (16.5)	9 (15.0)
Vomiting	4 (14.8)	28 (14.5)	4 (6.7)
Weight increased	.	4 (2)	1 (1.6)
Fall	4 (14.8)	18 (9.3)	3 (5.0)

The occurrence of these selected AEs of interest was generally highest in subjects in the 50-80kg weight category. The occurrence of nausea was interestingly lower in subjects in the <50kg weight range while the occurrence of vomiting in the >80kg range was less than half that of the other two weight groupings. The occurrence of falls does seem to clearly decrease with increasing body weight.

5.3.2 Study ENA713D2320

The sponsor references selected safety findings from Study D2320 which was the basis of the original approval of the 10cm^2 Exelon® Patch formulation. During this trial the 15cm^2 Exelon® Patch was used only as an intermediate titration step for subjects randomized to the 20cm^2 treatment arm. An outline of the study design as well as select efficacy and safety data is provided below.

Portions of both the efficacy and safety analysis from this study have been taken from Dr. Ranjit Mani's July 2, 2007 clinical review of the original submission of the study data.

5.3.2.1 Title

A 24-Week, Multi-Center, Randomized, Double-Blind, Placebo- And Active-Controlled, Parallel-Arm Evaluation Of The Efficacy, Safety, And Tolerability Of The Once-Daily Exelon® Patch Formulation In Patients With Probable Alzheimer's Disease (Mini-Mental Status Examination 10 – 20)

5.3.2.2 Objectives

5.3.2.2.1 Primary

To confirm the efficacy of the Exelon® patch in patients with probable Alzheimer's Disease (Mini-Mental Status Examination 10 to 20) by testing the following hypotheses:

- Exelon® target patch size of 20 cm^2 is superior to placebo on change from baseline at Week 24, simultaneously on the ADAS-Cog and ADCS-CGI-C
- Exelon® target patch size of 20 cm^2 is non-inferior to Exelon® capsule target dose of 12 mg on the change from baseline at Week 24 on the ADAS-Cog

- Exelon® target patch size of 10 cm^2 is superior to placebo on change from baseline at Week 24, simultaneously on the ADAS-Cog and ADCS-CGIC

- Exelon® target patch size of 20 cm^2 is superior to placebo on change from baseline at Week 24 on the ADCS-ADL

5.3.2.2.2 Secondary

To explore the efficacy, safety, and tolerability of Exelon® patch and capsules in patients with probable Alzheimer's disease (Mini-Mental Status Examination 10 to 20) by testing the following hypotheses:

- Exelon® target patch size (10 cm^2 and 20 cm^2) and Exelon® capsules are superior to placebo on change from baseline at Week 24 on:

    - Caregiver-based activities of daily living (ADCS-ADL)
    - Behavioral symptoms (Neuropsychiatry Inventory)
    - Brief, global cognitive testing (Mini-Mental Status Examination)
    - Executive function (Ten-point clock test)
    - Attention (Trailmaking Test Part A)
    - Caregiver satisfaction/preferences

- Exelon® target patch size of 20 cm^2 is superior to Exelon® capsule target dose of 12 mg on change from baseline at Week 24 on the ADAS-Cog, if non-inferiority has been demonstrated on the second primary objective.

- Exelon® patch and Exelon® capsule have comparable safety over 24 weeks of planned exposure, as measured by the incidence of adverse events, serious adverse events, and changes in vital signs. The Exelon® 10 cm^2 patch/day has superior tolerability to Exelon® capsules (12 mg/day) over 24 weeks of planned exposure, as measured by the incidence of gastrointestinal adverse events (particularly nausea and vomiting), the degree of burden (severity x incidence) of gastrointestinal adverse events (nausea and vomiting) and discontinuations due to gastrointestinal adverse events.

- All 4 sizes of Exelon® patches (5, 10, 15, 20 cm^2) have acceptable adhesion and skin irritation over 24 weeks of planned exposure.

- To collect pharmacokinetic information in Alzheimer's Disease patients receiving various patch sizes, using sparse sampling

- Pharmacogenetics: To explore whether individual genetic variation at the DNA level confers differential response to Exelon®. These include genetic factors that may relate to Alzheimer's Disease itself, predict response to treatment, predict susceptibility to drug-drug interactions, and predict genetic predisposition to clinically relevant or significant side effects

- Biomarkers: To conduct exploratory assays for novel proteins and other non-genetic elements of blood and urine that are associated with treatment response, or are possible correlates of disease severity or disease progression.

- To evaluate the safety and tolerability of Exelon® patch for up to 28 weeks of open-label treatment in patients with probable Alzheimer's Disease (Mini-Mental Status Examination score 10 to 20) who have completed the double-blind treatment phase of the study.

5.3.2.3 Design and Dose

This was to be a randomized, double-blind, placebo- and active-controlled, parallel- and four-arm, fixed-dose study.

The study was to have 4 treatment arms, as follows:

- Placebo
- Exelon® patch 10 cm^2 once daily
- Exelon® patch 20 cm^2 once daily
- Exelon® oral capsule 6 mg twice daily

Patients were to be titrated to their target (or maximum-tolerated) dose of Exelon® patch or oral capsule as follows:

- There were four consecutive ascending dose levels as indicated in the following table which is copied from Dr. Mani's review

Dose Level (DL)	Exelon® Patch	Exelon® Capsule
1	5 cm^2 QD	1.5 mg BID
2	10 cm^2 QD	3.0 mg BID
3	15 cm^2 QD	4.5 mg BID
4	20 cm^2 QD	6.0 mg BID

- Increases in dose were to be made every 4 weeks until the target dose or maximum-tolerated dose was reached.

Additional items of information are below.

The quantity of rivastigmine loaded in a single patch of each size was depicted in the table below which is copied from Dr. Mani's review.

Patch Size	Quantity of rivastigmine per patch
5 cm^2	9 mg
10 cm^2	18 mg
15 cm^2	27 mg
20 cm^2	36 mg

According to the sponsor, modeling data that included information from studies conducted with the same transdermal formulation of Exelon® and from studies with the capsule formulation suggested that:

- Exposure (AUC_{0-24}) with the 10 cm^2 patch is approximately equivalent to the capsule formulation administered in a daily dose of 7 to 8 mg
- Exposure (AUC_{0-24}) with the 20 cm^2 patch is approximately equivalent to the capsule formulation administered in a daily dose of 12 mg

Dose level adjustments were permitted during the maintenance period, in the event of poor tolerability in an effort to keep the patient on study drug. These were as follows (after the investigator had ensured that the patient is taking the capsule form of the study drug with meals):

- If tolerability was poor, the patch was to be removed and all doses of study drug avoided on the same and succeeding day(s), as recommended by the investigator

- Tolerability was to be re-evaluated after the recommended doses had been avoided. If the patient was better, and doses had been missed for ≤ 3 days, treatment could be restarted at the same dose level. If there remained concerns about the tolerability of the same dose level, treatment could be recommenced at the next lower dose level

- Titration could then be resumed using the same schedule, and doses could then be withheld if the drug was again poorly tolerated; if after the recommended period of dosage interruption, the patient's ability to tolerate the same dose was in question, study drug could be recommenced at the next lower dose level.

- Further attempts to titrate the dose upward could be made at the investigator's discretion (it was not necessary to achieve the target dose if that dose could not be tolerated)

- If a patient had not reached the target dose during the titration period, and if tolerability permitted, the investigator could resume titration during the maintenance period. However, if attempts to increase the dose were poorly tolerated, the previous highest well-tolerated dose level was to be resumed, and further dose increases avoided.

- Dose level decreases on account of poor tolerability are permitted at any time during the maintenance period.

Steps to be taken if dose interruption occurs on consecutive days were highlighted in the following sponsor table:

Consecutive Days Missed	Reason	Action
≤ 3	Any	Continue at the same DL, or restart at the next lower DL.
> 3	Tolerability problems	Retitrate starting at DL 1. Depending on past tolerability, dose increases may be performed at a minimum of 2-week interval
> 3	Other problem (e.g., medication not taken during a trip or patient illness)	Retitrate starting at DL 1 or restart at the next lower DL, depending on previous tolerability. Dose increases may be performed at a minimum of 2-week interval

The overall study design is also summarized in the following figure, copied from the submission:

Phase	**Pre-Randomization**		**Double-blind Treatment**				
			Exelon® Patch, Capsule or Placebo				
Period	Screening	Baseline*	Titration Period				Maintenance**
Week	Wk -4 to -1	Wk 0	1-4	5 - 8	9 - 12	13 -16	17-24
Visit	V1	V2	V3	V4	V5	V6	V7 or PD
Treatment	None		**Group A:** Exelon® patch titrated from 5 to 10 cm^2 patch size				10 cm^2 Exelon® patch size
			Group B: Exelon® patch titrated from 5 to 10, 15, and 20 cm^2 patch size				20 cm^2 Exelon® patch size
			Group C: Exelon® capsule titrated from 3 to 6, 9 and 12 mg/d				12 mg/d Exelon® capsule
			Group D: Placebo				Placebo

* Study medication will be started on the day after the baseline visit

** The maintenance dose is defined as the target patch size for the treatment group or the highest well-tolerated dose for each individual patient.

PD: Premature discontinuation

The period of double-blind treatment was to be followed by a 28-week period of open-label treatment (extension protocol) in all patients who had previously completed the double-blind phase. The extension protocol would involve 12 weeks of dose titration and 16 weeks of maintenance treatment. All patients entering the extension study were to receive the patch only and were to be titrated to their maximum tolerated dose using the same titration schedule used for the double-blind phase.

5.3.2.4 Duration

24 weeks of double-blind parallel-arm treatment.

5.3.2.5 Sample Size

1040 patients randomized equally to the 4 treatment groups (260 patients per group).

5.3.2.6 Selection

5.3.2.6.1 Key Inclusion Criteria

- Male or female
- Age: 50-85 years
- Dementia of the Alzheimer's Type by DSM IV criteria
- Probable Alzheimer's disease by NINCDS-ADRDA criteria. The brain imaging procedure (CT scan or MRI) used to establish that these criteria have been met must have been done within 1 year prior to randomization.
- Mini-Mental Status Examination score of 10-20
- If female, must be surgically sterile or at least one year post-menopausal
- Sufficient education to read, write, and communicate effectively during the pre-morbid state
- Reliable caregiver
- Written informed consent from patient, legal representative (if applicable), and witness (if applicable)
- Capable of complying with the requirements of the study

5.3.2.6.2 Key Exclusion Criteria

- Any advanced, severe or unstable disease that could interfere with study evaluations or put patient at special risk
- Any disability that interferes with completion of study requirements
- Any medical or neurological condition, other than Alzheimer's Disease, that could explain the patient's dementia
- Current diagnosis of possible or probable vascular dementia (NINDSAIREN criteria)
- Score of > 4 on the modified Hachinski Ischemic Scale
- Active uncontrolled peptic ulceration, or gastrointestinal bleeding, within the previous 3 months

- Bradycardia (< 50 beats per minute), sick sinus syndrome, conduction deficits (S-A block, second or third degree A-V block)

- Clinically significant urinary tract obstruction

- Severe or unstable cardiovascular disease

- Current diagnosis of acute, severe, or unstable obstructive lung disease

- A history within the past year or current diagnosis of cerebrovascular disease

- Current diagnosis of active, uncontrolled seizure disorder

- Current DSM-IV diagnosis of major depression; patients may be included if currently on antidepressant therapy that does not have anticholinergic effects, have improved and are stable for at least 4 weeks.

- Any other DSM-IV Axis I diagnosis that may interfere with the patient's response to study medication, including other primary degenerative dementia, schizophrenia or bipolar disorder

- A known exaggerated pharmacological sensitivity or hypersensitivity to drugs similar to rivastigmine or other cholinergic compounds

- History of allergy to topical compounds containing Vitamin E

- Current diagnosis of an active skin disorder or lesion that would prevent accurate assessment of the adhesion and skin irritation potential of the patch

- Previous lack of efficacy with cholinesterase inhibitors

- Use of any of the following substances prior to randomization:

    - Any investigational drug during the 4 weeks prior to screening
    - A drug or treatment known to cause major organ toxicity during the previous 4 weeks
    - Hypnotics including zolpidem or zopiclone within the previous 24 hours, unless chronic stable doses of these medications were to be used.
    - Approved or unapproved cholinesterase inhibitors, "other approved treatments for Alzheimer's Disease," or memantine during the previous 4 weeks.
    - Succinylcholine-type muscle relaxants during the two weeks prior to randomization
    - Centrally-acting anticholinergic drugs during the preceding 4 weeks
    - Selegiline during the previous 4 weeks
    - Peripherally-acting anticholinergics, not taken at a stable dose, within the previous 4 weeks
    - Any new psychotropic medication, or dopaminergic agent or any psychotropic medication or dopaminergic agent not taken at a stable dose during the previous 4 weeks

- Lithium during the past 2 weeks

5.3.2.6.3 Prohibited Concomitant Medications

As outlined in the exclusionary criteria above.

5.3.2.7 Schedule

The following table, copied from the submission, outlines the schedule of study procedures:

Phase		Pre-Randomization		Double- Blind Treatment				
Period	C [a]	SCR	BL	Titration				Maintenance
Visit Week		-4 to -1	0	1-4	5-8	9-12	13-16	17-24
Visit		V1	V2	V3	V4	V5	V6	7* or PD
Screening Information								
Screening Log / Informed Consent	S	X						
Inclusion/exclusion Criteria	S	X	X					
DSM-IV / Criteria for dementia of the Alzheimer's type	S	X	X					
NINCDS/ADRDA Criteria for Probable AD	S	X	X					
MRI / CT Scan	S	X						
MHIS	S	X						
Lab. Diagnostic Screening Tests	D	X						
ECG	~~S~~ D	X						X
Physical and Neurological Exam	S [b]	X	X [d]					
Demographic/Baseline Charac.								
Demography and Background Info.	D	X						
Medical History/Current Conditions	D	X	X					
Treatment Assessments								
Drug Dispensing Label	S		X	X	X	X	X	
Dosage Administration Record	D			X	X	X	X	X
Prior/conc. Medications/CNS Related	D	X	X	X	X	X	X	X
Treatment compliance	S			X	X	X	X	X
Efficacy Assessments								
ADAS-Cog	D [c]	X	X				X	X
ADCS-CGIC	D		X				X	X
ADCS-ADL	D		X				X	X
NPI (including NPI-D)	D		X				X	X
MMSE	D [c]	X	X				X	X
Ten Points Clock Test	D		X				X	X
Trail Making Test (Part A)	D		X				X	X
Safety Assessment								
Adverse Events	D			As needed				
Serious AE's	D	As needed						
Vital Signs	D	X	X	X	X	X	X	X
Laboratory Tests	D	X	X [d]					
Skin Irritation and Adhesion								
Patch Adhesion Assessment	D			X	X	X	X	X
Skin Irritation Assessment	D			X	X	X	X	X
Other								
ADCPQ Satisfaction/Preference	D		X		X			X
Pharmacokinetic Sample	D							X
Pharmacogenetic Sample	D	X [e]						

5.3.2.8 Outcome Measures

5.3.2.8.1 Primary Efficacy Measures

- ADAS-Cog
- ADCS-CGIC
- ADCS-ADL

5.3.2.8.2 Secondary Efficacy Measures

- NPI
- MMSE
- Ten-Point Clock Test
- Trailmaking Test Part A

5.3.2.8.3 Safety Measures

Adverse events, vital signs, electrocardiograms

5.3.2.8.4 Pharmacokinetic Measures

Plasma levels of rivastigmine and NAP 226-90 (the principal metabolite of rivastigmine)

5.3.2.9 Safety Monitoring

Adverse events, vital signs, skin irritation assessment

5.3.2.10 Analysis Plan

5.3.2.10.1 General

5.3.2.10.2 Study Populations

All randomized patients who receive at least one dose of study medication and have at least a pre- and post-baseline assessment for one of the primary efficacy variables.

All randomized patients who received at least one dose of study medication and have at least a pre- and post-baseline assessment for one of the primary efficacy variables.

All randomized patients who received at least one dose of study medication and had at least one safety assessment following baseline.

5.3.2.10.3 Demographic and Baseline Characteristics

Data for these characteristics were to be presented by treatment group and country using summary statistics.

5.3.2.10.4 Treatment Compliance, Exposure to Study Drug, and Concomitant Medications

These data were to be presented using summary statistics.

5.3.2.10.5 Primary Efficacy Parameters

Two separate types of primary efficacy analysis were stipulated a priori by the sponsor, as agreed upon at a Pre-NDA Meeting with this Division that was held on November 8, 2005.

- The first of these types of analysis addressed the original 4 study hypotheses and was planned (b) (4) This type of analysis is described below under the heading "Original Proposed Primary Efficacy Analysis"

- The second type of primary efficacy analysis was designed to meet this Agency's requirements for approval and addressed only two of the 4 original study hypotheses. This type of analysis is described below under the heading "Alternative Primary Efficacy Analysis" in bold font

5.3.2.10.5.1 Originally Proposed Primary Efficacy Analysis

As noted earlier, (b) (4).

5.3.2.10.5.1.1 Original Study Hypothesis

Four study hypotheses were to be evaluated in the same numerical order as below.

5.3.2.10.5.1.1.1 First Study Hypothesis

This (superiority) hypothesis involved the comparison of the 20 cm^2 Exelon® patch with placebo on both the ADAS-Cog and ADCS-CGIC. In order to demonstrate the superiority of the 20 cm^2 Exelon® patch over placebo, a statistically significant difference favoring placebo would need to be shown on both parameters.

5.3.2.10.5.1.1.2 Second Study Hypothesis

(b) (4)

5.3.2.10.5.1.1.3 Third Study Hypothesis

This (superiority) hypothesis involved the comparison of the 10 cm^2 Exelon® patch with placebo on both the ADAS-Cog and ADCS-CGIC. In order to demonstrate the superiority of the 10 cm^2 Exelon® patch over placebo, a statistically significant difference favoring placebo would need to be shown on both parameters.

5.3.2.10.5.1.1.4 Fourth Study Hypothesis

(b) (4)

5.3.2.10.5.1.2 Strategy for Confirmatory Testing of Each Study Hypothesis

The steps to be taken in the testing process were to be as follows:

Step 1: The superiority of the 20 cm^2 Exelon® patch over placebo was to be demonstrated simultaneously for both primary efficacy variables, the ADAS-Cog and ADCS-CGIC. If for both treatment comparisons, the corresponding 2-sided p-values were less than 0.05, then the superiority of the 20 cm^2 Exelon® patch over placebo was to be regarded as confirmed and it would then be possible to proceed to Step 2. Otherwise the testing procedure was to be stopped, and none of the confirmatory hypotheses established

(b) (4)

Step 3: The superiority of the 10 cm^2 Exelon® patch over placebo was to be demonstrated simultaneously for both primary efficacy variables, the ADAS-Cog and ADCS-CGIC. If for both treatment comparisons, the corresponding 2-sided p-values are less than 0.05, then the superiority of the 10 cm^2 Exelon® patch over placebo was to be regarded as confirmed and it would then be possible to proceed to Step 4. Otherwise the testing procedure was to be stopped, and no further confirmatory hypothesis considered capable of being established.

(b) (4)

5.3.2.10.6 Additional Efficacy Analyses

A detailed review of the protocol's approach to the other aspects of the efficacy analysis (e.g., secondary efficacy measures, subgroup analyses, etc) is beyond the scope of this review and will therefore not be discussed herein.

5.3.2.10.7 Analysis of Safety Parameters

- The safety parameters were to be adverse events, vital signs, and skin irritation index. All were to be described by treatment group using summary statistics

- Adverse events were to be coded using the MedDRA dictionary and presented (number and proportion) by treatment group, body system, and individual event, and also grouped according to severity, relationship to study medication, and outcome. Serious adverse events and adverse event discontinuations were to be tabulated. The occurrence of gastrointestinal adverse events (nausea and vomiting), the patient's mean daily degree of burden (defined) due to such adverse events, and discontinuations due to gastrointestinal adverse events were also to be tabulated and analyzed using the Cochran-Mantel-Haenszel test for binary response with country as stratification to compare all treatment groups.

- For vital signs (including body weight), summary statistics were to be presented by treatment for baseline and post-baseline evaluations as well as the number and proportion of patients with clinically notable abnormalities. Clinically notable abnormalities of body weight were to be flagged in data listings

- For electrocardiograms, summary statistics will be presented by treatment for baseline and post-baseline evaluations as well as the number and proportion of patients with abnormal values. Treatment-emergent abnormalities are to be listed.

- For the skin irritation index, summary statistics were to be provided by time, treatment group and patch size using the intent-to-treat observed cases population.

5.3.2.11 Results

As previously noted, on the highlights of the trial's findings will be presented below. Specifically, a summary of the analyses of the co-primary efficacy measures as well as a high-level summary of the key safety findings will be discussed.

5.3.2.11.1 Patient Disposition

The following table, copied from the current submission, summarizes the disposition of patients who were enrolled in the trial:

Table 1-13 Patient disposition by treatment group (Study D2320- Exelon 20 cm^2 patch, 10 cm^2 patch and placebo groups)

Disposition/Reason	Exelon 20 cm^2 n (%)	Exelon 10 cm^2 n (%)	Placebo n (%)
Total number of patients			
Randomized	303 (100.0)	293 (100.0)	302 (100.0)
Exposed to study drug	303 (100.0)	291 (99.3)	302 (100.0)
Completed	241 (79.5)	229 (78.2)	266 (88.1)
Discontinued	62 (20.5)	64 (21.8)	36 (11.9)
Reasons for discontinuation			
Adverse event(s)	26 (8.6)	28 (9.6)	15 (5.0)
Subject withdrew consent	19 (6.3)	21 (7.2)	6 (2.0)
Death	5 (1.7)	4 (1.4)	3 (1.0)
Unsatisfactory therapeutic effect	4 (1.3)	3 (1.0)	6 (2.0)
Lost to follow-up	4 (1.3)	3 (1.0)	3 (1.0)
Administrative problems	2 (0.7)	1 (0.3)	2 (0.7)
Protocol violation	2 (0.7)	3 (1.0)	1 (0.3)
Abnormal laboratory value(s)	0 (0.0)	1 (0.3)	0 (0.0)
Subject's condition no longer required study drug	0 (0.0)	0 (0.0)	0 (0.0)

Exelon capsule data from Study D2320 are not be presented, since the comparator of interest for the Exelon 15 cm^2 patch is the approved Exelon 10 cm^2 patch.

Reasons for discontinuation are presented in descending frequency, as reported in Exelon 20 cm^2 patch group.

5.3.2.11.2 Demographics

The following table, copied from the current submission, summarizes the demographics of the study population enrolled in Study D2320 by treatment group:

Table 1-10 Demographics characteristics by treatment (Study D2320 - Safety population - Exelon 20 cm^2 patch, 10 cm^2 patch and placebo groups)

Demographic variable	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Placebo N = 302 n (%)
Age group (years)			
< 65	38 (12.5)	36 (12.4)	31 (10.3)
≥ 65	265 (87.5)	255 (87.6)	271 (89.7)
Age (years)			
Mean (SD)	74.2 (7.7)	73.6 (7.9)	73.9 (7.3)
Median	76.0	75.0	75.0
Range	50-88	50-90	50-89
Gender – n (%)			
Male	103 (34.0)	93 (32.0)	101 (33.4)
Female	200 (66.0)	198 (68.0)	201 (66.6)
Race – n (%)			
Caucasian	227 (74.9)	220 (75.6)	227 (75.2)
Black	3 (1.0)	1 (0.3)	2 (0.7)
Oriental	27 (8.9)	25 (8.6)	27 (8.9)
Other	46 (15.2)	45 (15.5)	46 (15.2)
Body weight (kg)			
Mean (SD)	66.4 (13.0)	67.3 (12.9)	66.2 (13.5)
Range	34.0 – 119.0	35.0 - 109.0	40.8 – 113.0

Exelon capsule data from Study D2320 are not be presented, since the comparator of interest for the Exelon 15 cm^2 patch is the approved Exelon 10 cm^2 patch.

5.3.2.11.3 Exposure

The following table, copied from the current submission, summarizes the duration of exposure (in weeks) by treatment group in the D2320 safety population:

Duration of exposure (weeks)	Exelon 20 cm^2 N = 303	Exelon 10 cm^2 N = 291	placebo N = 302
Mean duration	22.0	21.4	23.0
SD	(5.5)	(6.3)	(4.2)
Median duration	24.0	24.0	24.0
Range	0.6-35.0	0.1-30.4	0.4-26.9

SD = Standard deviation

5.3.2.11.4 Summary of Primary Efficacy Results

The following tables, copied from the clinical study report for Study D2320, summarize the results of the efficacy analysis for both of the trial's co-primary outcome measures, respectively:

ADAS-cog

Visit			Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon Capsule N = 256	Placebo N = 282
Week 16		n	257	248	253	280
	Baseline	Mean	27.5	27.0	27.9	28.5
	Post-baseline	Mean	26.1	26.1	27.4	28.5
	Change	Mean	-1.4	-0.8	-0.5	-0.0
		p-value	0.007*	0.090	0.274	
Week 24		n	262	248	253	281
	Baseline	Mean	27.4	27.0	27.9	28.6
	Post-baseline	Mean	25.8	26.4	27.3	29.5
	Change	Mean	-1.6	-0.6	-0.6	1.0
		p-value	<0.001*	0.005*	0.003*	

Only patients with a valid baseline and post-baseline score at Week 16 or Week 24 were included
Negative change score indicates improvement.
p-values are derived from two-way analyses of covariance and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

ADCS-CGIC

Visit	Exelon 20 cm^2 N = 264	Exelon 10 cm^2 N = 251	Exelon capsule N = 256	Placebo N = 282
Week 16 – n (%)				
Markedly improved (1)	3 (1.2)	4 (1.6)	1 (0.4)	1 (0.4)
Moderately improved (2)	21 (8.2)	24 (9.7)	20 (8.0)	22 (8.1)
Minimally improved (3)	58 (22.7)	48 (19.4)	48 (19.3)	53 (19.4)
Unchanged (4)	109 (42.7)	104 (42.1)	111 (44.6)	116 (42.5)
Minimally worse (5)	40 (15.7)	53 (21.5)	43 (17.3)	53 (19.4)
Moderately worse (6)	20 (7.8)	14 (5.7)	23 (9.2)	25 (9.2)
Markedly worse (7)	4 (1.6)	0 (0.0)	3 (1.2)	3 (1.1)
n	255	247	249	273
mean	3.9	3.9	4.0	4.0
SD	1.13	1.08	1.10	1.10
p-value	0.177	0.195	0.804	
Week 24 – n (%)				
Markedly improved (1)	5 (1.9)	5 (2.0)	3 (1.2)	2 (0.7)
Moderately improved (2)	32 (12.3)	29 (11.7)	29 (11.5)	26 (9.4)
Minimally improved (3)	48 (18.5)	43 (17.3)	60 (23.7)	50 (18.0)
Unchanged (4)	94 (36.2)	105 (42.3)	96 (37.9)	91 (32.7)
Minimally worse (5)	50 (19.2)	41 (16.5)	30 (11.9)	65 (23.4)
Moderately worse (6)	27 (10.4)	22 (8.9)	30 (11.9)	36 (12.9)
Markedly worse (7)	4 (1.5)	3 (1.2)	5 (2.0)	8 (2.9)
n	260	248	253	278
mean	4.0	3.9	3.9	4.2
SD	1.27	1.20	1.25	1.26
p-value	0.054	0.010*	0.009*	

p-values are derived from CMH test (van Elteren test) blocking for country and are based on comparison of each Exelon treatment group with placebo.
* $p < 0.05$

5.3.2.11.5 Key Efficacy Conclusions with Respect to the 20cm^2 Exelon® Patch

A detailed review of the entirety of the trial's efficacy results is not germane to the conduct of the current review and will therefore not be discussed herein. Rather, a summary of the conclusions drawn by both Dr. Mani and Dr. Tristan Massie, the Biometric reviewer for the submission, will be summarized.

In brief, Dr. Massie raised several concerns regarding the results of the primary analysis comparing the effect of the 20 cm^2 Exelon® Patch with placebo on the ADCS-CGIC. Ultimately, Dr. Massie concluded that the 20cm^2 patch failed to show a clear advantage in efficacy when compared to the 10cm^2 patch.

Similarly, Dr. Mani concluded that the results of the study did provide sufficient evidence of the efficacy of the 20 cm^2 and 10 cm^2 patches of Exelon® over placebo on both primary efficacy measures, (b) (4)

5.3.2.11.6 Summary of Key Selected Safety Results

As outlined above, the 15cm^2 Exelon® Patch was solely used as a titration step for a period of 4 weeks during Study D2320. As such, pooling of the safety data from Studies D2320 and D2340 would be largely inappropriate due to the differences in the trial designs. The sponsor has rather elected to present relevant data from both Study D2320 and D2340 in a comparative format. It will exclusively be this data that will be the subject of the limited safety review of Study D2320 presented below.

5.3.2.11.6.1 Adverse Events

The table below, copied from the submission, summarizes a comparison of the adverse event data from the first 24 weeks of the DB phase of Study D2340 and the complete 24 weeks of Study D2320. This table only presents adverse event data from the two target treatment arms (10cm^2 and 20cm^2) from Study D2320.

Table 2-3 Number (%) of patients with AEs (at least 3% in any treatment group) by preferred term and study treatment group (first 24 weeks of Study D2340 DB phase and 24-week Study D2320) - Safety population

	Study D2340		Study D2320		
	Exelon Patch 15 cm^2 (W 0-24) N=280 n (%)	Exelon Patch 10 cm^2 (W 0-24) N=283 n (%)	Exelon Patch 20 cm^2 N=303 n (%)	Exelon Patch 10 cm^2 N=291 n (%)	Placebo N=302 n (%)
Preferred term					
Nausea	27 (9.6)	10 (3.5)	64 (21.1)	21 (7.2)	15 (5.0)
Vomiting	25 (8.9)	8 (2.8)	57 (18.8)	18 (6.2)	10 (3.3)
Application site erythema	16 (5.7)	13 (4.6)	1 (0.3)*	1 (0.3)*	0 (0.0)*
Decreased appetite	15 (5.4)	6 (2.1)	27 (8.9)	9 (3.1)	6 (2.0)
Diarrohea	14 (5.0)	12 (4.2)	31 (10.2)	18 (6.2)	10 (3.3)
Fall	12 (4.3)	10 (3.5)	7 (2.3)	6 (2.1)	10 (3.3)
Agitation	11 (3.9)	9 (3.2)	7 (2.3)	3 (1.0)	6 (2.0)
Application site pruritus	10 (3.6)	8 (2.8)	1 (0.3)*	2 (0.7)*	0 (0.0) *
Headache	10 (3.6)	10 (3.5)	13 (4.3)	10 (3.4)	5 (1.7)
Dizziness	8 (2.9)	1 (0.4)	21 (6.9)	7 (2.4)	7 (2.3)
Depression	8 (2.9)	8 (2.8)	12 (4.0)	11 (3.8)	4 (1.3)
Weight decreased	7 (2.5)	4 (1.4)	23 (7.6)	8 (2.7)	4 (1.3)
Hypertension	7 (2.5)	5 (1.8)	4 (1.3)	2 (0.7)	11 (3.6)
Anxiety	6 (2.1)	5 (1.8)	8 (2.6)	9 (3.1)	4 (1.3)
Insomnia	5 (1.8)	3 (1.1)	12 (4.0)	4 (1.4)	6 (2.0)
Abdominal pain	3 (1.1)	4 (1.4)	11 (3.6)	7 (2.4)	2 (0.7)
Asthenia	2 (0.7)	4 (1.4)	9 (3.0)	4 (1.4)	3 (1.0)

Exelon capsule data from Study D2320 are not be presented, since the comparator of interest for the Exelon 15 cm^2 patch is the approved Exelon 10 cm^2 patch.

For study D2340, the population used is the Safety-DB population.

Preferred terms are sorted by descending frequency of Exelon Patch 15cm^2 column in study D2340.

A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

* *In Study D2320, signs of skin irritation at the patch application sites were not documented as adverse events but were recorded in the Skin Irritation Rating eCRF. If a patient prematurely discontinued from the study due to skin irritation or if the local skin irritation fulfilled the criteria of a SAE, the skin irritation was to be recorded as an adverse event*

The occurrence of gastrointestinal AEs was lower for the Exelon 10cm^2 arm in Study D2340 as compared to Study D2320. This finding is not unexpected in that subjects in Study D2340 had already been taking the 10cm^2 patch from between 24-48 weeks prior to enrollment into the DB phase of the trial. Therefore, these subjects would be expected to either have become more tolerant to these AEs over time or have withdrawn if the respective AEs had been intolerable. In general, AEs were dose-dependent based on this comparison with the incidences for the AEs of nausea, vomiting, and diarrhea being over twice as common in the 20cm^2 arm of Study D2320 as compared to the 15cm^2 arm of Study D2340.

5.3.2.11.6.2 Deaths, Other Serious Adverse Events, and Discontinuations due to Adverse Events

The following sponsor table, copied from Dr. Mani's review, summarizes the number and proportion of patients in each treatment group who died, had serious adverse events (SAEs), or discontinued due to adverse events (AEs):

Patients with serious or significant AEs	Exelon 20 cm^2 N = 303 n (%)	Exelon 10 cm^2 N = 291 n (%)	Exelon capsule N = 294 n (%)	Placebo N = 302 n (%)
Deaths	5 (1.7)**	4 (1.4)*	2 (0.7)	3 (1.0)#
SAEs	36 (11.9)	23 (7.9)	21 (7.1)	26 (8.6)
Discontinued due to AEs	31 (10.2)	31 (10.7)	25 (8.5)	18 (6.0)
Discontinued due to SAEs	12 (4.0)	12 (4.1)	7 (2.4)	9 (3.0)
Discontinued due to non-serious AEs	20 (6.6)	19 (6.5)	19 (6.5)	9 (3.0)

* An additional patient died from cardiac arrest 7 days after discontinuation due to an SAE of delirium
** One patient died whilst receiving 5 cm^2 patch treatment (no up-titration had occurred)
# An additional patient died from cardiac arrest 17 days after discontinuation of study treatment

Although not reproduced here, Dr. Mani reviewed the details of each of the categories outlined in the preceding table and concluded that there was no clear reason to associate these findings with an effect of the treatment (either patch or capsule).

5.3.2.11.6.3 Adverse Events of Interest

As previously noted in this review, the tablet formulation of Exelon® has been associated with a high incidence of nausea and vomiting, leading to a bolded warning in the current product labeling for that formulation.

Dr. Mani indicated in his review that the overall incidence of nausea and vomiting, and of discontinuations due to nausea and vomiting, was highest in the Exelon® 20 cm^2 and Exelon® capsule groups, as indicated by the following table which is copied from that review:

Parameter	Treatment Group			
	Exelon® 20 cm^2	Exelon® 10 cm^2	Exelon® Capsule	Placebo
Total N	303	291	294	302
Nausea and/or vomiting – N (%)	84 (27.7)	32 (11.0)	84 (28.6)	20 (6.6)
Discontinuations due to nausea and/or vomiting – N (%)	8 (2.6)	2 (0.7)	8 (2.7)	4 (1.3)

The following table, copied from the submission, directly compares the adverse event data (for AEs of interest) from Studies D2320 and D2340 for the initial 4 weeks of exposure to the 15cm^2 patch following titration from the 10cm^2 patch:

Table 2-5 Number of patients with adverse events of interest during the 4 weeks after titration from Exelon 10 cm^2 to 15 cm^2 dose (Studies D2340 and D2320) – Safety population

	Patients titrated from 10 cm^2 to 15 cm^2 dose		
Study	**Study D2340**	**Study D2320**	
Treatment arm	15 cm^2	20 cm^2	Placebo
Dose	15 cm^2	15 cm^2	
4-week observation period	Weeks 1-4 of DB maintenance Period[1]	Weeks 9-12 of DB titration period[2]	Weeks 9-12 of DB titration period
N	280	285	293
	n (%)	n (%)	n (%)
AE preferred term			
Nausea	18 (6.4)	20 (7.0)	3 (1.0)
Vomiting	14 (5.0)	13 (4.6)	2 (0.7)
Diarrhea	3 (1.1)	7 (2.5)	3 (1.0)
Dizziness	3 (1.1)	6 (2.1)	0 (0.0)

[1] Patients titrated to Exelon 15 cm^2 patch following ≥20 treatment with Exelon 10 cm^2 patch (Study D2340)
[2] Patients titrated to Exelon 15 cm^2 patch following 4 weeks treatment with Exelon 10 cm^2 patch (Study D2320)
A patient with multiple occurrences of an AE under one treatment in one study period is counted only once in the AE category for that treatment during the study period. If the AE had repeated onsets in different study periods, the AE is counted once in each of these study periods.
MedDRA 14.0 was used for Study D2340; MedDRA 8.1 was used for Study D2320

As the table suggests, the frequency of these AEs were largely equivalent in this comparison. The difference in the rates of diarrhea and dizziness, albeit higher in Study D2320, are based on a low overall number of events and therefore unlikely to be meaningful.

5.3.2.11.6.4 Additional Safety Analyses

Although not reproduced herein, Dr. Mani concluded that there were no clinical significant concerns raised with respect to the additional safety analyses conducted during the trial including vital signs, electrocardiograms, or skin irritation assessments.

6 Summary of Efficacy

The data that have been provided with this submission in support of the efficacy of the 15cm^2 Exelon® Patch are derived solely from Study D2340. The key aspects of this trial are briefly outlined in the following table:

Objectives	Design	Dose	Population	Sample Size	Duration	Efficacy Outcome Measures
Primary: Assess the change from DB baseline to Week 48 in	An initial 24-48 week IOL phase at a target dose of a 10cm^2	IOL: 10cm^2 DB 10cm^2 or 15cm^2	Mild to moderate AD (MMSE10-24)	IOL: 1585 DB: 567 (randomized)	IOL: 24-48 weeks DB:48 weeks	Primary: Change from DB baseline to Week 48 of the DB treatment phase in ADAS-cog total score

function and cognition	patch. Patients who demonstrated cognitive decline in the IOL phase were then randomized into a 48-week DB treatment phase to receive either the $10cm^2$ or $15cm^2$ patch.		Enrollment in DB phase required a decline in the IOL phase at either Weeks 24, 36, or 48			and ADCS-IADL total score <u>Secondary:</u> • Time to decline on ADCS-IADL in DB treatment phase • Trailmaking Test change from BL to Week 48 in DB treatment phase • NPI score at Week 48 in DB treatment phase

Study D2340 was notable in that the duration selected for the primary analyses of the efficacy endpoints was at Week 48 of the DB treatment phase. This is an atypically long duration for a trial designed to assess a symptomatic effect in AD. The vast majority of trials designed for this purpose have ranged from between 12-24 weeks which has proven consistently adequate. In fact, even study D2320 which was pivotal in the initial approval of the $5cm^2$ and $10cm^2$ patches, was 24 weeks in duration. The submission indicates that the sponsor's review of the existing literature, along with additional internal data, factored into the selection of the 48 week duration of Study D2340. Regardless of this rationale, the fact remains that this prolonged duration relative to the historical standard has presented challenges in the ultimate interpretation of the trial's findings as will be detailed below.

The co-primary efficacy outcome measures for Study D2340 were the change from DB baseline to Week 48 of the DB treatment phase in the ADAS-cog and ADCS-IADL scores. The primary analysis of these endpoints was based on the ITT-DB population using LOCF to account for missing values. Point estimates (difference in least square means) and corresponding 95% confidence intervals for the difference between treatment groups based on an ANCOVA model were reported. The following tables, copied from the submission, summarize the key efficacy findings with respect to the ADCS-IADL and ADAS-cog, respectively, in the ITT-DB LOCF population:

Table 4-2 Change from DB baseline in ADCS-Instrumental ADL score in the double-blind phase, by treatment group and population

Population Visit		Exelon 15 cm²		Exelon 10 cm²		Exelon 15 cm² - Exelon 10 cm²		
		n	Mean	n	Mean	DLSM	95% CI	p-value
ITT(DB) – LOCF	Baseline	265	27.5	271	25.8			
DB -Week 8	Value	265	27.3	271	25.0			
	Change	265	-0.2	271	-0.8	0.8	(-0.2, 1.9)	0.114
DB -Week 12	Value	265	27.5	271	25.4			
	Change	265	0.1	271	-0.4	0.7	(-0.5, 1.8)	0.252
DB -Week 16	Value	265	26.7	271	24.0			
	Change	265	-0.7	271	-1.8	1.3	(0.2, 2.5)	0.025*
DB -Week 24	Value	265	26.0	271	22.9			
	Change	265	-1.5	271	-2.8	1.7	(0.5, 2.9)	0.005*
DB -Week 32	Value	265	25.2	271	21.7			
	Change	265	-2.2	271	-4.0	2.1	(0.9, 3.4)	<0.001*
DB -Week 48 (primary endpoint)	Value	265	23.1	271	19.6			
	Change	265	-4.4	271	-6.2	**2.2**	**(0.8, 3.6)**	**0.002***

Table 4-3 Change from baseline in ADAS-cog score in the 48-week double-blind phase, by treatment group and population

Population Visit		Exelon 15 cm²		Exelon 10 cm²		Exelon 15 cm² - Exelon 10 cm²		
		n	Mean	n	Mean	DLSM	95% CI	p-value
ITT(DB) - LOCF	Baseline	264	34.4	268	34.9			
DB - Week 12	Value	264	34.2	268	35.5			
	Change	264	-0.2	268	0.6	-0.9	(-2.0, 0.1)	0.091
DB - Week 24	Value	264	35.4	268	37.1			
	Change	264	1.0	268	2.2	-1.3	(-2.5, -0.2)	0.027*
DB -Week 48 (primary endpoint)	Value	264	38.5	268	39.7			
	Change	264	4.1	268	4.9	**-0.8**	**(-2.1, 0.5)**	**0.227**

As demonstrated in the preceding tables, the trial failed to meet one of its pre-specified co-primary efficacy endpoints: the difference between treatment groups in the change from DB baseline to Week 48 of the DB treatment phase in ADAS-cog scores in the DB-ITT LOCF population [DLSM of -0.8 (-2.1, 0.5) p=0.227]. The trial did successfully meet the other pre-specified co-primary efficacy endpoint: the difference between treatment groups in the change from DB baseline to Week 48 of the DB treatment phase in ADCS-IADL scores in the DB-ITT LOCF population [DLSM of 2.2 (0.8, 3.6) p=0.002].

The difference between treatment groups in the change from Baseline in ADAS-cog scores was, however, statistically significant at Week 24 [DLSM of -1.3 (-2.5, -0.2) p=0.027]. This finding in particular further calls into question the selection of the 48 week duration for the DB treatment phase of the trial. As outlined in detail previously in this review, the number of subjects who dropped out of the trial between Weeks 24-48 of the DB treatment phase was significant (29 and 45 in the 15cm^2 and 10cm^2 arms, respectively) and could easily have contributed to the lack of a statistically significant difference on ADAS-cog scores at Week 48. The similar effect sizes that were observed on the ADAS-cog at the 24 and 48 week timepoints further suggests that the lack of statistical significance is this period could have been a result of attrition. This high percentage of drop-outs is not at all unexpected in this population, particularly in that subjects

had already participated in the IOL phase of the trial for up to 48 weeks prior to enrollment in the DB phase. This fact becomes even more relevant in that the trial also failed to reach its planned enrollment of 410 subjects/treatment group in the DB phase.

The treatment groups failed to statistically separate on any of the trial's secondary efficacy endpoints.

Ultimately, the critical question in this review centers on whether the lack of a statistically significant difference between treatment groups on ADAS-cog scores at DB Week 48 in Study D2340 would definitely preclude the overall conclusion that the 15cm^2 Exelon® Patch could still provide a meaningful benefit to patients beyond what is offered by the already marketed 10cm^2 patch. My conclusion is that the efficacy findings from Study D2340 do still support the approval of the 15cm^2 Exelon® Patch. This conclusion is based on several relevant considerations which are outlined below.

First, and perhaps the most important contributing factor to my conclusion, is the fact that Study D2340 was comparing the 15cm^2 Exelon® Patch to an active comparator (the 10cm^2 patch) and not placebo. Therefore, it can only be concluded that the 15cm^2 patch failed to provide an additional cognitive benefit over the 10cm^2 patch at Week 48. It cannot, however, be assumed that there was a lack of *any* overall benefit from the 15cm^2 patch at that timepoint as the study was not designed for that purpose. Unfortunately, there is no well-controlled clinical trial data to offer an insight as to how much benefit over placebo an acetylcholinesterase inhibitor may offer following up to 96 weeks of treatment (IOL + DB phases). The comparison of the 15cm^2 patch to an active comparator allows though for the reasonable conclusion that some patients may still benefit from the higher dose patch when view in the context of the entirety of the efficacy findings from Study D2340. I would again turn to the analogy that has been already outlined in this review between the current situation and a hypothetical dose-ranging efficacy trial involving the 15cm^2 and 10cm^2 patches in comparison to placebo. In that scenario, the lack of a statistically significant difference between the treatment groups on a single co-primary endpoint would not necessarily prohibit the approval of the higher dose. Rather, that individual finding would need to be considered in the context of the totality of the study's results.

Second (and closely tied to the previously consideration), there are several examples of regulatory precedent that would support the application of that line of reasoning in this current instance. In clinical trials with the acetylcholinesterase inhibitor Aricept™, for example, the studies in patients with mild to moderate AD failed to show a statistically significant difference between the 5 and 10mg doses on the trial's measure of global functioning (the CIBIC+). Both doses were superior to placebo on the CIBIC+, however. More recently, a 23mg dose of Aricept™ was approved based on a single 24-week trial that compared that dose to the already marketed 10mg dose in patients with moderate to severe AD. There was no placebo group in that trial. Similar to the current submission, that trial failed to demonstrate a statistically significant difference between the treatment arms on one of the study's co-primary endpoints (also the CIBIC+). The 23mg dose did statistically separate from the 10mg dose on the cognitive measure (the SIB) was statistically at Week 24. Among the Agency's principle interpretations was that since Aricept™ 10mg was known to be an effective dose in that population it could be reasonably assumed that the 23mg dose would also have at least a similar benefit at 24 weeks with respect to the CIBIC+. Finally, in a clinical trial of another approved cholinesterase inhibitor drug, Razadyne (galantamine hydrobromide), a 24 mg dose of

the immediate-release drug did not show a statistically significant improvement in CIBIC+ scores over a 16 mg dose, but the label states that "[i]t is possible . . . that a daily dose of 24 mg of RAZADYNE® might provide additional benefit for some patients."

Finally, based on the results of Study D2340, the 15cm^2 patch was able to demonstrate an additional benefit after 24 weeks of treatment over the 10cm^2 patch in subjects who were found to be decliners despite treatment with the 10cm^2 patch for between 24-48 weeks. For reasons previously discussed, even a 24 week trial would be at the long end of the historical standard range for an investigation of a symptomatic treatment for AD. Therefore, while a benefit at an interim timepoint in a 12 week trial may have little clinical meaning, a treatment effect after a 24 week period in a 48 week trial could still be considered to confer a meaningful benefit to patients.

It should not go unmentioned that the effect sizes outlined in the tables above that were observed on both the ADAS-cog and the ADCS-IADL scales are admittedly small. That said, these differences are consistent with what has been observed in the whole of the currently approved treatments for Alzheimer's disease. It is precisely for this reason that the Division holds that a co-primary assessment of function (or a global clinical rating) is used to verify the clinical meaningfulness of these changes for patients.

Ultimately, it was the integration of the aforementioned factors (i.e. use of an active comparator, regulatory precedent, and the statistically significant benefit at Week 24) that led to my conclusion that efficacy findings from Study D2340 support approval of the 15cm^2 Exelon® Patch.

7 Summary of Safety

Since its approval in 2000, the oral formulations of Exelon® have been widely used in the United States (US) for the treatment of Alzheimer's disease. Exelon® has also been used in the US to treat the dementia associated with Parkinson's disease since its approval for that indication in 2006. Similarly, the 5 and 10cm^2 doses of the Exelon® Patch have also been commonly prescribed for these indications since their US approval in 2007. Subsequent to these approvals, there have been no new safety signals identified with the use of Exelon® in particular or acetylcholinesterase inhibitors as a class, in the postmarket setting. Therefore, the goal of this safety review was to determine whether the safety profile of the 15cm^2 Exelon® Patch was sufficiently acceptable to support its approval.

The principal focus of the safety analysis of Study D2340 relates to the frequency of the adverse events known to be related to the use of Exelon®. Specifically, the occurrence of gastrointestinal adverse events is commonly associated with the use of acetylcholinesterase inhibitors and Exelon® in particular (with rates as high as 47 and 31% for nausea and vomiting, respectively that have been observed in the clinical trials of the Exelon® capsule in AD). As anticipated, gastrointestinal AEs were also the most common AEs associated with treatment in Study D2340 occurring at an incidence of 36.43 and 28.98% in the 15cm^2 and 10cm^2 treatment arms, respectively. In particular, vomiting was observed in 12.86 versus 7.77% (+ 5.09%) of subjects in the 15cm^2 arm as compared to the 10cm^2 arm. Nausea was also observed in 15.00

versus 6.71% (+ 5.09%) of subjects in the 15cm^2 arm as compared to the 10cm^2 arm. As detailed in Section 5.3.1.13.5.3.1 of this review, while the occurrence of severe nausea (0.4%) and vomiting (1.8%) in the 15cm^2 treatment arm was low, the incidence of nausea and vomiting of both mild and moderate severity were roughly equivalent.

The incidences of deaths in Study D2340 were similar between treatment groups with no deaths being obviously associated with treatment. Similarly, the incidences of SAEs were similar between treatment groups and largely consistent with conditions know to be intercurrent to an Alzheimer's disease patient population. The overall incidence of discontinuations due to adverse events was lower in the 15cm^2 treatment arm as compared to the 10cm^2 arm (9.6 versus 12.7%, respectively). The most significant difference in these discontinuations relates to the occurrence of vomiting (1.79 versus 0.35% in the 15cm^2 and 10cm^2 groups, respectively). The overall numbers of subjects affected in these groups were only 5 and 1, however.

There were no clinically concerning findings overall, or between treatment groups, with respect to vital signs, body weight, or electrocardiogram results in Study D2340.

An analysis of the time dependency of the adverse events of interest in Study D2340 suggests that nausea and vomiting in particular were most frequent in the first 4 weeks of the use of the 15cm^2 Exelon® Patch in Study D2340 (6.4 and 5.0%, respectively) and tended to decrease over time (4.1 and 2.5%, respectively, after 24 weeks of treatment).

As discussed in detail in Section 5.3.2.11.6 the results of Study D2320, which used the 15cm^2 Exelon® Patch as a 4 week titration step, were discussed briefly in comparison to the safety findings from Study D2340. When these results were viewed in the context of the findings from the 20cm^2 treatment group in Study D2320, there was an obvious dose-response relationship apparent between AEs thought to be associated with treatment (i.e., gastrointestinal AEs). The rates of AEs of interest between subjects treated with the 15cm^2 patch in both trials were roughly equivalent.

In conclusion, no new safety signals were identified with the use of the Exelon® Patch in Study D2340. The adverse events of interest appeared to be dose-related with higher incidences observed in the 15cm^2 treatment arm as compared to the 10cm^2 arm. On the whole, these adverse events were mild to moderate in severity and tended to resolve over time. They were also not a substantial cause of SAEs or discontinuation from the trial. Furthermore, the occurrence of nausea and vomiting were significantly below those observed in the pivotal trials for the currently marketed oral formulations of Exelon®. Therefore, the safety findings provided in the current submission are acceptable in order to support the approval of the 15cm^2 Exelon® Patch.

8 Postmarket Experience

According to the submission, Exelon® capsules and oral solution have been approved in 93 and 65 countries, respectively. The Exelon® 5 cm^2 and 10 cm^2 patch have been approved in 83 and 82 countries, respectively. Additionally the 15 cm^2 patch and 20 cm^2 patch have been approved in 8 countries and the 15 cm^2 patch was commercially launched in Brazil in November 2009. In

Japan, 2.5 cm^2, 5 cm^2, 7.5 cm^2 and 10 cm^2 sizes have been recently approved (April 2011) for the treatment of mild to moderate AD.

The cumulative patient exposure since the first launch of the product is estimated to be approximately (b) (4) patient-years for the oral formulation and approximately (b) (4) patient-years for the patch formulation. The estimate of patient exposure for Exelon® oral formulation is calculated based on worldwide sales volume in kilogram (kg) of active drug substance sold divided by the defined daily dose (DDD). The DDD for Exelon® oral formulation is 6 mg. This estimate includes the patients exposed in non-interventional postmarketing studies.

There have been no additional unexpected safety signals that have emerged in the postmarket setting with regard to any of the formulations of Exelon®. It should be noted, however, that in 2011 the Agency did require the sponsor to adapt one of the diagrams related to patch application instructions in the Patient Information section of labeling. This action was taken in order to address reports of patients who had been administered multiple patches at once as a possible result of misinterpreting that diagram (which showed all of the possible application sites on a single image simultaneously).

9 Appendices

9.1 Literature Review/References

Not applicable.

9.2 Labeling Recommendations

9.2.1 Office of Surveillance and Epidemiology Review

A Label, Labeling, and Packaging review was completed by the Division of Medication Error Prevention and Analysis (DMEPA) reviewer on June 26, 2012. That review urged that the following recommendations be implemented by the sponsor prior to the approval of this NDA supplement:

A Carton Labeling

1. Medication errors associated with wrong route of administration have been reported in post-marketing use. Relocate the route of administration statement, "For Transdermal Use Only", which is currently on the back panel of the carton labeling and pouch label to the principal display panel directly below the statement of strength to reinforce the proper route of administration for this product. Additionally, we recommend this labeling revision be implemented on the 4.6 mg/24 hours and 9.5 mg/24 hours carton labeling at the time of the next printing.

B Foil Pouch Label

2. Include the statement "Change the location of each new patch" on the back panel of the foil pouch label following the statement "Apply patch to intact skin immediately after removal from pouch". To allow space for this statement, relocate the route of administration statement to the principal display panel (See Comment A1 above). Additionally, we recommend this labeling revision be implemented on the 4.6 mg/24 hours and 9.5 mg/24 hours foil pouch labeling at the time of the next printing.

9.2.2 Clinical Labeling Review

On December 28, 2011 the Division provided with the sponsor with an edited version of the existing approved label for the 5 and 10cm^2 Exelon® Patch dosages. These edits were intended to bring the label further into compliance with the Physician's Labeling Rule (PLR) format as well as to more clearly convey the relevant information contained therein. The

sponsor was also asked to resubmit to proposed label with references to the inclusion of the 15cm^2 Exelon® Patch to this application based on the backbone of the December 28, 2011 letter from the Division. On February 14, 2012 the sponsor has submitted the requested labeling to this NDA supplement along with a series of additional counter-proposals. As the majority of these changes (b) (4) to the 15cm^2, (b) (4) will be reviewed (b) (4)

The proposals in the sponsor's label that deal directly with the inclusion of the 15cm^2 Exelon® Patch appear largely acceptable. Internal discussions, however, have not been completed at the time of this review. The sponsor's description of Study D2340 is reasonable. The key clinical edits to the updated label would include a clarification that an increase to the 15cm^2 patch should not be attempted until a patient has been treated for at least 4 weeks on the 10cm^2 dose. These changes were made to both the **DOSAGE AND ADMINISTRATION** and **HIGHLIGHTS OF PRESCRIBING INFORMATION** sections of the label.

9.3 Advisory Committee Meeting

Not applicable.

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/s/

NICHOLAS A KOZAUER
08/07/2012

RANJIT B MANI
08/07/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

CHEMISTRY REVIEW(S)

OFFICE OF NEW DRUG QUALITY ASSESSMENT

Review of Chemistry, Manufacturing, and Controls

Clinical Review Division: Neurology Products (HFD-120)

NDA#: 22-083	**REVIEW#.** 1	**REVIEW DATE:**	08/30/2012
SUBMISSION TYPE	**DOCUMENT DATE**	**CDER DATE**	**ASSIGNED**
S-016 (PA)	10/28/2011	10/31/2011	11/09/2011
AMENDMENT	**PDUFA GOAL**		
04/04/2012			
04/12/2012	08/31/2012		
07/06/2012			
07/13/2012			
08/17/2012			
08/23/2012			
08/28/2012			

NAME & ADDRESS OF APPLICANT: Novartis Pharmaceutical Corporation
One Health Plaza
East Hanover, NJ 07936

Peter D. McArdle, Director, Drug Regulatory Affairs.
Phone: (862) 778-3228
Fax: (973) 781-3310

DRUG PRODUCT NAME

Proprietary:	Exelon Patch
Nonproprietary/USAN:	rivastigmine
Code Name#:	ENA713D
Chem. Type:	
Ther. Class:	

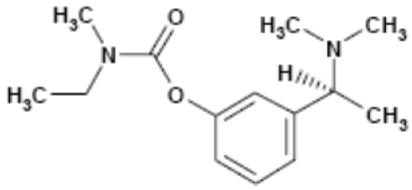
PHARMACOLOGICAL CATEGORY/INDICATION: Dementia (Alzheimer's Type); mild to moderate dementia associated w/Parkinson's Disease

DOSAGE FORM: TDS
STRENGTH: 4.6 mg/24 hours, 9.5 mg/24 hours

ROUTE OF ADMINISTRATION: transdermal
DISPENSED: __X_ Rx ___ OTC
SPECIAL PRODUCTS: ___ Yes _X_ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

Chemical Name: (S)-3-[1-(Dimethylamino)ethyl] phenyl ethylmethylcarbamate
Molecular Formula: $C_{14}H_{22}N_2O_2$
Molecular Weight: 250.34



REMARKS/COMMENTS:

The efficacy supplement provides for a new dose strength of the transdermal formulation (13.3 mg/24 hours nominal release rate, 27 mg total drug load, 15 cm^2 patch size) for use in the currently approved indications for the treatment of mild to moderate dementia of the Alzheimer's type and for the treatment of mild to moderate dementia associated with Parkinson's disease. Currently, two strengths are approved, 4.6 mg/24 hours (9 mg drug loading, 5 cm^2 patch size) and 9.5 mg/24 hours (18 mg drug loading, 10 cm^2 patch size).

The original NDA covers (b) (4) strengths (9 mg/5 cm^2, 18 mg/10 cm^2) (b) (4) and the CMC information was reviewed by Dr. Sherita McLamore and found acceptable for approval. However, (b) (4) strengths (9 mg/5 cm^2, 18 mg/10 cm^2) were approved (b) (4). Following approval of these two strengths, a number of CMC changes for the drug product have been approved, including alternate DP manufacturing site at LTS Lohmann Therapy Systems Corp, West Caldwell NJ, and DP analytical testing site at Novartis Pharmaceuticals Corp at Suffern, NY. The CMC information for the new dose strength of the Exelon Patch submitted in this efficacy supplement is essentially the same as that (b) (4) in the original NDA and the following approved supplements, except for a minor change in the drug product microbial specification and an improved release liner (b) (4) The rest of the specification items (acceptance criteria and analytical methods) (b) (4)

The review covers the (b) (4) issue of the patch, change in the release liner, batch analysis and stability data of the new strength, as well as the labeling. After several rounds of information requests/teleconferences, the applicant agreed to include a qualitative specification on (b) (4).

The applicant stated that the change in release liner from (b) (4) was reported in the 2010 Annual Report, which does not have any technical information. Upon information request, the applicant responded that the (b) (4)

The batch analysis and stability results of the new strength appear acceptable. The applicant provided labeling information for the immediate container and carton, as well as package insert, the information presented in the labeling appears acceptable.

Overall, the supplement is recommended for approval from CMC standpoint.

CONSULT REVIEW:

On 05/31/2012, Product Quality Microbiology (Denise Miller) NAI'ed the supplement. Per her comment, there are no quality microbiological concerns for this supplement based on the information provided.

The Biopharmaceutics review (dated 8/30/2012) by Tapash Ghosh recommends approval of the supplement.

COMMENTS/REQUESTS TO BE CONVEYED TO APPLICANT:

N/A

CONCLUSIONS & RECOMMENDATIONS:

The efficacy supplement is recommended for approval from CMC standpoint.

(see attached electronic signature page)

Zedong Dong, Ph.D.
Review Chemist

Terrance Ocheltree, Ph.D.
Division Director
ONDQA Division II

cc: Orig. NDA#22-083
HFD-120/Division File
ONDQA/DIV I/PM/TBouie
ONDQA/DIV II/TOcheltree
ONDQA/DIV I/Chem/ZDong

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZEDONG DONG
08/30/2012

TERRANCE W OCHELTREE
08/30/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 22-083 S046
Drug Name:	Exelon® patch (rivastigmine)
Indication:	Mild to moderate Alzheimer's Disease
Applicant:	Novartis Pharmaceuticals
Date of Submission:	10/28/2011
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Jingyu (Julia) Luan, Ph.D. (HFD-710)
Concurring Reviewers:	Kun Jin, Ph.D. (HFD -710) H.M. James Hung, Ph.D. (HFD -710)
Medical Division:	Division of Neurology Product (HFD -120)
Clinical Team:	Nicholas Kozauer, M.D. (HFD-120) Ranjit Mani, M.D. (HFD-120)
Project Manager:	Teresa Wheelous (HFD-120)
Keywords:	Active control, co-primary endpoints, ANCOVA

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1 EXECUTIVE SUMMARY

This submission includes a single phase III pivotal efficacy study CENA713D2340 (Study D2340). Based on the results of Study D2340, the trial demonstrated a statistically significant effect on ADCS-Instrumental ADL (the co-primary global endpoint, p=0.002); however, the treatment difference on ADAS-cog (the co-primary cognitive endpoint) was not statistically significant (p=0.227). Since for Alzheimer's Disease the trial usually needs to win on both cognitive and global endpoints for an efficacy claim, there is no sufficient statistical evidence to support the efficacy of Exelon 15 cm^2 patch in the treatment of mild to moderate Alzheimer's Disease, compared to Exelon 10 cm^2 patch.

Study D2340 was a prospective, multicenter, randomized, double-blind (DB), double-dummy, parallel group study in patients with mild to moderate dementia of the Alzheimer's type. The study was designed to compare the efficacy and safety of treatment with Exelon 15 cm^2 patch to Exelon 10 cm^2 patch during a 48 week DB treatment phase in patients who demonstrated functional and cognitive decline after 24 to 48 weeks of treatment with Exelon 10 cm^2 patch during an Initial Open Label (IOL) period. This study was conducted in Canada, France, Germany, Italy, Spain, Switzerland, and the United States.

The study consisted of the following phases: Screening phase (up to 5 weeks), IOL phase (24-to 48 weeks), DB phase (48 weeks), and Extended open-label (EOL) phase (48 weeks). There were 1979 patients screened for this study. A total of 1582 patients were enrolled into the IOL phase and exposed to study drug. At the end of the IOL phase, 567 patients were classified as decliners and randomized into the DB phase. Of the 567 randomized patients, 410 patients (72.3%) completed the study. The study completion rates were similar between the treatment groups, 70.7% for Exelon 10 cm^2 group and 73.9% for Exelon 15 cm^2 group.

The co-primary efficacy analysis variables were the change from DB randomization baseline to DB Week 48 in the ADAS-cog total score and ADCS-Instrumental ADL score. Both co-primary outcome variables were analyzed using Analysis of Covariance (ANCOVA) model adjusted for country and baseline score. The primary analysis was based on the ITT-DB population using last observation carried forward (LOCF) to account for missing values. The p-value for ADAS-cog was 0.227 and the p-value for ADCS-Instrumental ADL was 0.002. The results of various sensitivity analyses, including non-parametric analysis and MMRM analysis, were consistent with those of the pre-specified primary efficacy analyses. The nominal p-values for the three secondary efficacy variables were not statistically significant. Please refer to Section 3.2.1 for details.

For this study, LOCF was used to handle missing data in the primary efficacy analyses, which was previously agreed between the sponsor and the Agency at the study design stage. According to a recent publication, "*The prevention and treatment of missing data in clinical trials*" by the National Academies, LOCF as primary efficacy analysis is discouraged. However, for this particular study, since the results of LOCF analysis are consistent with those of various sensitivity analyses, using LOCF in the primary efficacy analyses doesn't affect the interpretation of the efficacy results.

Treatment effect was further analyzed by country. The treatment effect was defined as the difference between the mean change from baseline of Exelon 15 cm^2 and mean change from baseline of Exelon 10 cm^2. For ADAS-cog, the point estimates of treatment effect were in the same direction as the overall patients for United States, Germany, and Spain. In this study, fifty-four percent (54%) of the patients were randomized in these three countries. In contrast, for Canada, France, Switzerland, and Italy, the mean change from baseline in ADAS-cog at Week 48 for Exelon 15 cm^2 group was numerically larger than that for Exelon 10 cm^2 group. The difference in the treatment effect among countries isn't surprising as the p-value for this co-primary endpoint didn't reach statistical significance (p=0.227). For ADCS-Instrumental ADL, the point estimates of treatment effect were in the same direction as the overall patients except for Canada. The US ITT-DB population represents 38% of the total ITT-DB population (N=206/536). For US ITT-DB population only, based on the pre-specified primary efficacy analyses, the p-value for ADAS-cog was 0.1706 and the p-value for ADCS-Instrumental ADL was 0.0017. Please refer to Section 3.2.2.2 for detailed analyses.

2 INTRODUCTION

2.1 Overview

Alzheimer's Disease (AD) is a neurodegenerative disorder that is characterized by gradual onset of memory impairment, aphasia, apraxia, agnosia and/or disturbance of executive functioning with continuing cognitive decline and functional impairment. This is due to progressive impairment in the cortically projecting cholinergic system. Cholinesterase inhibitors, which act by inhibiting the degradation of acetylcholine in functionally intact cholinergic synapses and in the brain parenchyma, form the mainstay of therapy for AD.

The treatment goals for AD are to slow the progression of disease, although current orally administered AD treatments are effective in lessening the severity of symptoms such as memory loss and confusion.

Exelon® (rivastigmine) is a slowly reversible (pseudo-reversible), brain selective, dual inhibitor of acetylcholine- and butyrylcholine- esterase of the carbamate type. Exelon exerts its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible cholinesterase inhibition.

The once-daily Exelon transdermal patch was approved in the United States (US; NDA 22083, Serial No. 000) for the treatment of mild to moderate dementia of the Alzheimer's type and for the treatment of mild to moderate dementia associated with Parkinson's disease. It is available in 2 sizes, a 5 cm^2 patch and a 10 cm^2 patch.

Study CENA713D2340 (Study D2340) is a randomized, double-blind (DB) study designed to evaluate the comparative safety and efficacy of the Exelon 15 cm^2 patch as compared to the Exelon 10 cm^2 patch in the treatment of patients with mild to moderate dementia of the

Alzheimer's type, who had demonstrated functional and cognitive decline while treated with Exelon 10 cm^2 patch for up to 48 weeks. This study was conducted in Canada, France, Germany, Italy, Spain, Switzerland, and the United States.

2.2 Data Sources

The sponsor's electronic submission was stored in the directory of \\Cdsesub1\evsprod\NDA022083\0046 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis quality are generally acceptable.

3.2 Evaluation of Efficacy

3.2.1 PROTOCOL ENA713D2340

3.2.1.1 Study Objectives

The objectives of the study were to compare the efficacy, safety and tolerability of Exelon 10 cm^2 patch vs. Exelon 15 cm^2 patch in patients who have demonstrated cognitive decline in the initial open-label (IOL) phase (Exelon 10 cm^2 patch).

3.2.1.2 Study Design

This was a prospective, multicenter, randomized, double-blind (DB), double-dummy, parallel group study in patients with mild to moderate dementia of the Alzheimer's type. The study was designed to compare the efficacy and safety of treatment with Exelon 15 cm^2 patch to Exelon 10 cm^2 patch during a 48 week DB treatment phase in patients who demonstrated functional and cognitive decline after 24 to 48 weeks of treatment with Exelon 10 cm^2 patch during a prior IOL period.

The study consisted of the following phases:

- Screening phase (up to 5 weeks)
- IOL phase (24-to 48-weeks): Patients were initially treated with Exelon 5 cm^2 patches for 4 weeks, and subsequently titrated to Exelon 10 cm^2 patches. Patients were evaluated at Weeks 24, 36, and 48 of the IOL for functional decline and cognitive decline (MMSE decrease of $\geq$2 from the previous visit OR $\geq$3 points from IOL baseline (Day 1))
- DB phase (48 weeks): Patients who demonstrated decline during the IOL phase were randomized in equal proportions to 1 of 2 treatment arms (Exelon 10 cm^2 or Exelon 15 cm^2 patches).

- Extended open-label (EOL) phase (48 weeks): Patients who did not demonstrate decline after 48 weeks in the IOL phase were offered continued treatment with a maintenance dose of Exelon 10 cm^2.

An outline of the study design is presented in Figure 1.

Figure 1: Study Design

Phase	Screening		Initial open-label						Double-blind treatment				
Visit	1	2	3	4	5	6	7	8	1.1	1.2	1.3	1.4	1.5
Week	< -5	Day 1	4	8	12	24	36	48	4	12	24	36	48*

		Titration	Maintenance	Additional	Maintenance for decliners
					Exelon 10 cm^2 patch
		Exelon 5 cm^2	Exelon 10 cm^2 patch with demonstrated decline at Week 24, 36 or 48		Exelon 15 cm^2 patch
Treatment	None				Extended open-label for (non-decliners)
					Visit 3.1 3.2 3.3 3.4
					Week 12 24 36 48
			Exelon 10 cm^2 patch without demonstrated decline at Week 48		Exelon 10 cm^2 patch

Baseline for the initial open-label (IOL) treatment phase was Day 1 prior to first dose. Baseline for the double-blind (DB) treatment phase was the DB randomization day.

Additional visits were allowed for patients without demonstrated functional and cognitive decline during IOL maintenance visits.

Patients randomized to the DB treatment phase began treatment with DB medication on the day following randomization. Down-titration was allowed as required to address tolerability problems.

* or premature discontinuation visit.

Source: Figure 9-1 of sponsor's Clinical Study Report

3.2.1.3 Efficacy Measures

The co-primary efficacy analysis variables are the change from DB randomization baseline to DB Week 48 in the ADAS-cog total score and ADCS-Instrumental ADL score.

The ADAS-cog subscale is comprised of 11 items that are summed to a total score ranging from 0 to 70, with lower scores indicating less severe impairment. It was administered by a mental health professional who had a minimum of 2 years research experience, and had achieved certification after completing rater training.

The ADCS-Instrumental ADL scale is a caregiver-based scale composed of 23 items developed for use in dementia clinical studies. It is designed to assess the patient's performance of both basic and instrumental activities of daily living, however, in this study only the ADCS-Instrumental ADL (items 7-23) was used. The ADCS-Instrumental ADL total score ranged from 0 to 56, with higher scores indicating less severe impairment.

The secondary efficacy evaluation is based on:

- Time to functional decline. It is defined by either a ≥1 point decrease in ADCS-Instrumental ADL score in a visit and confirmed by the following visit/assessment or ≥2 points decrease from DB-baseline and still ≥1 point less at the subsequent confirmation visit.
- Trail Making Test (TMT Parts A and B). TMT provides information on visual search, scanning, speed of processing, mental flexibility, and executive functions. The TMT consists of 2 parts. TMT-Part A requires an individual to draw lines sequentially connecting 25 encircled numbers distributed on a sheet of paper. Task requirements are similar for TMT-Part B except the person must alternate between numbers and letters (e.g., 1, A, 2, B, 3, C, etc.). The score on each part represents the amount of time required to complete the task. A negative change score indicates an improvement in condition.
- Neuropsychiatric Inventory-10 (NPI-10).The NPI assesses a wide range of behaviors encountered in dementia patients to provide a means of distinguishing frequency and severity of behavioral changes, and facilitates rapid behavioral assessment through the use of screening questions. Ten behavioral domains are evaluated through an interview of the caregiver by a mental health professional. The scale includes both frequency (range: 1-4) and severity (range: 1-3) ratings of each domain as well as a composite domain score (frequency x severity). Each domain has a maximum score of 12 (0 means not present). The sum of the composite scores for the 10 domains yields the NPI-10 total score. Thus, the range for the total score is 0 to 120.

3.2.1.4 Statistical Analysis Plan

3.2.1.4.1 Analysis Data Sets

The following patient populations were used for the analyses in double-blind treatment phase:

- All randomized population (RND) - This population includes all randomized patients who entered the DB phase.
- Intent to treat population (ITT-DB) - This population includes all patients who were randomized, received at least 1 dose of study drug during the DB phase, and had at least 1 post-randomization assessment for both co-primary efficacy variables (ADAS-cog, ADCS-Instrumental ADL) in the DB phase.
- Safety population (Safety-DB) - This population includes all patients who were randomized, received at least 1 dose of study drug during the DB phase and had at least 1 post-randomization safety assessment during the DB phase.
- Per protocol population (PP-DB) - This population includes all randomized patients who received at least 1 dose of study drug during the DB phase, had at least 1 post-randomization efficacy assessment for both co-primary efficacy variables (ADAS-cog, ADCS-Instrumental ADL) on or after DB-Week 24 on the target dose, and had no major protocol deviations during the DB phase.

3.2.1.4.2 Analyses for Co-primary Efficacy Variables

For both co-primary outcome variables (ADAS-cog and ADCS-Instrumental ADL), the statistical analysis was based on the change from DB-baseline to DB-Week 48 of the total score.

Both co-primary outcome variables were analyzed using Analysis of Covariance (ANCOVA) model adjusted for country and baseline score. The primary analysis was based on the ITT-DB population using last observation carried forward (LOCF) to account for missing values.

As supportive analyses, the primary ANCOVA analyses were also performed for the observed cases (OC) based on ITT-DB population, and with LOCF and with OC based on PP-DB population. In addition, the comparison of treatment groups was also performed using the non-parametric van Elteren test stratified by country to assess the robustness of the results of the primary analysis based on ITT-DB with LOCF. This is also referred to as rank ANCOVA. As additional sensitivity analysis, a mixed-effects repeated measures model (MMRM) was used.

3.2.1.4.3 Analyses for Secondary Efficacy Variables

Time to Functional Decline

The analysis was carried out for the ITT-DB and the PP-DB populations. Analysis of time to functional decline was performed using the log-rank test for interval censored data. The percentage of patients who showed functional decline in the ADCS-Instrumental ADL were summarized and compared between dose groups by means of a Cochran Mantel Haenszel (CMH) test with country as a stratification variable based on ITT-DB and on PP-DB populations using OC.

Trail Making Test (Parts A and B)

The parameters for analysis were the change from DB-baseline to DB-Week 48 in total time to perform each part (TMT Part A and TMT Part B). These parameters were analyzed using Analysis of Covariance (ANCOVA) model adjusted for country and baseline score, based on the ITT-DB population with LOCF and with OC.

Neuropsychiatric Inventory-10 (NPI-10)

The parameter for analysis was the change from DB-baseline to DB-Week 48 in the NPI-10 total score in the DB phase. A negative change score indicates an improvement in condition (symptom reduction). These parameters were analyzed using Analysis of Covariance (ANCOVA) model adjusted for country and baseline score, based on the ITT-DB population with LOCF and with OC.

3.2.1.4.4 Changes in the Planned Analysis

Changes in the planned analyses are minor and don’t impact the interpretation of the efficacy results.

3.2.1.5 Patient Disposition, Demographic and Baseline Characteristics

3.2.1.5.1 Patient Disposition

There were 1979 patients screened for this study. A total of 1582 patients were enrolled into the IOL phase and exposed to study drug. At the end of the IOL phase, 567 patients were classified as decliners and randomized into the DB phase; however 1 of these patients was randomized in

error and did not receive DB study treatment. The patient disposition for the double-blind phase is presented in Table 1 .

Table 1: Patient Disposition in the Double-blind Phase

Disposition/Reason	Exelon 15 cm^2 N = 280 n (%)	Exelon 10 cm^2 N = 287 n (%)	Total N = 567 n (%)
Double-blind (DB) treatment phase			
Randomized	280 (100.0)	287 (100.0)	567 (100.0)
Exposed to study drug in the DB phase	280 (100.0)	286 (99.7)	566 (99.8)
Completed the DB phase	207 (73.9)	203 (70.7)	410 (72.3)
Discontinued the DB phase	73 (26.1)	83 (28.9)	156 (27.5)
Reason for discontinuation			
Adverse event(s)	28 (10.0)	33 (11.5)	61 (10.8)
Death	3 (1.1)	5 (1.7)	8 (1.4)
Unsatisfactory therapeutic effect	13 (4.6)	13 (4.5)	26 (4.6)
Protocol deviation(s)	3 (1.1)	5 (1.7)	8 (1.4)
Lost to follow-up	6 (2.1)	4 (1.4)	10 (1.8)
Subject withdrew consent	17 (6.1)	20 (7.0)	37 (6.5)
Administrative problem(s)	2 (0.7)	3 (1.0)	5 (0.9)
Subject's condition no longer requires study drug	1 (0.4)	0 (0.0)	1 (0.2)

Percentage (%) is calculated based on the Randomized population.
Source: PT-Table 14.1-1.1b

Source: Table 10-2 of sponsor's Clinical Study Report

The number of patients in each analysis set is shown in Table 2.

Table 2: Number (%) of patients in Analysis Populations

Population			Total n (%)
Open-label phases (Exelon 10 cm^2 treatment)			
Enrolled			1584 (100.0)
Safety - initial open-label (SAF-IOL)			1582 (99.9)
Intent to treat - initial open-label (ITT-IOL)			1518 (95.8)
Safety - extended open-label (SAF-EOL)			457 (28.9)
Intent to treat - extended open-label (ITT-EOL)			416 (26.3)
Double-blind treatment phase	**Exelon 15 cm^2 n (%)**	**Exelon 10 cm^2 n (%)**	**Total n (%)**
Randomized to the double-blind phase	280 (100.0)	287 (100.0)	567 (100.0)
Intent to treat - double-blind (ITT-DB)	265 (94.6)	271 (94.4)	536 (94.5)
Safety - double-blind (SAF-DB)	280 (100.0)	283 (98.6)	563 (99.3)
Per protocol - double-blind (PP-DB)	194 (69.3)	214 (74.6)	408 (72.0)

For the open-label phases, the percentages (%) are calculated based on the Enrolled population.
For the double-blind phase, the percentages (%) are calculated based on the Randomized population.
Source: PT-Table 14.1-2.1

Source: Table 11-1 of sponsor's Clinical Study Report

3.2.1.5.2 Demographic and Other Baseline Characteristics

Table 3 presents demographics for the randomized population (N=567). The majority of patients who entered the DB phase were female (64.7%) and most patients were more than 65 years of age (90.8%), which is consistent with this condition. The majority of patients were Caucasian (96.6%), which reflects the population in the participating countries. Overall, the treatment groups for the DB phase were similar with respect to the DB-baseline demographics, except that the Exelon 15 cm^2 group had a higher proportion of patients younger than 65 years of age (12.1% vs. 6.3% in the lower dose treatment group).

Table 3: Patient Demographic Characteristics (Randomized Population)

Demographic Characteristic Category / statistic		Exelon 15 cm^2 N = 280	Exelon 10 cm^2 N = 287	Total N = 567
Gender - n (%)	Male	95 (33.9)	105 (36.6)	200 (35.3)
	Female	185 (66.1)	182 (63.4)	367 (64.7)
Race - n (%)	Caucasian	266 (95.0)	282 (98.3)	548 (96.6)
	Black	8 (2.9)	2 (0.7)	10 (1.8)
	Oriental	2 (0.7)	1 (0.3)	3 (0.5)
	Other	4 (1.4)	2 (0.7)	6 (1.1)
Age (years)	n	280	287	567
	Mean (SD)	75.61 (7.365)	75.88 (6.787)	75.74 (7.073)
	Median	77.50	77.00	77.00
	Range	54.0 - 87.0	53.0 - 87.0	53.0 - 87.0
Age group - n (%)	< 65 years	34 (12.1)	18 (6.3)	52 (9.2)
	≥ 65 years	246 (87.9)	269 (93.7)	515 (90.8)
Weight (kg)	n	280	287	567
	Mean (SD)	69.47 (15.501)	67.93 (13.893)	68.69 (14.716)
	Median	69.35	67.00	68.00
	Range	38.0 - 118.4	40.0 - 110.6	38.0 - 118.4
Weight category (kg) - n (%)	< 50	27 (9.6)	24 (8.4)	51 (9.0)
	50 to 80	193 (68.9)	209 (72.8)	402 (70.9)
	> 80	60 (21.4)	54 (18.8)	114 (20.1)
BMI (kg/m^2)	n	279	282	561
	Mean (SD)	25.98 (4.776)	25.42 (4.407)	25.70 (4.599)
	Median	25.60	24.90	25.30
	Range	16.4 - 49.3	16.0 - 44.8	16.0 - 49.3

N = Number of patients in the Randomized population.
n = Number of patients meeting the criterion (for categorical variables) or the number of patients with a non-missing assessment (for continuous variables).
Body Mass Index (BMI) = weight (kg) / height (m) ^{2}.
Demographic characteristics at double-blind baseline, which is the last assessment in the initial open-label phase are presented.
Source: PT-Table 14.1-3.1b

Source: Table 11-4 of sponsor's Clinical Study Report

Table 4 shows patient background characteristics for the randomized population. For patients who entered the DB phase, the mean and median duration of time since the first AD symptom and since the first diagnosis by a physician were slightly shorter in the Exelon 15 cm^2 group than in the lower dose treatment group. There were no important differences in other background characteristics assessed.

Table 4: Patient Background Characteristics (Randomized Population)

Background characteristics Category / statistic		Exelon 15 cm^2 N = 280	Exelon 10 cm^2 N = 287	Total N = 567
Patient's relatives with AD - n (%)	Mother	49 (17.5)	49 (17.1)	98 (17.3)
	Father	19 (6.8)	21 (7.3)	40 (7.1)
	Sibling	38 (13.6)	37 (12.9)	75 (13.2)
	Other	28 (10.0)	25 (8.7)	53 (9.3)
	None	175 (62.5)	186 (64.8)	361 (63.7)
Time since first symptom of AD was noticed by patient/caregiver (years) [a]	n	280	287	567
	Mean (SD)	3.86 (2.780)	4.31 (2.765)	4.09 (2.779)
	Median	3.20	3.60	3.40
	Range	0.2 - 17.7	0.3 - 15.6	0.2 - 17.7
Time since first symptom of AD was first diagnosed by physician (years) [a]	n	280	287	567
	Mean (SD)	1.80 (1.821)	2.04 (2.136)	1.92 (1.988)
	Median	1.25	1.40	1.30
	Range	0.0 - 10.9	0.0 - 12.6	0.0 - 12.6
Number of years of formal education	n	279	287	566
	Mean (SD)	10.5 (3.97)	10.6 (3.99)	10.6 (3.97)
	Median	12.0	11.0	11.0
	Range	2.0 - 20.0	3.0 - 22.0	2.0 - 22.0
MMSE [b]	n	280	287	567
	Mean (SD)	14.1 (4.79)	14.2 (4.58)	14.2 (4.68)
	Median	14.0	14.0	14.0
	Range	0.0 - 24.0	2.0 - 26.0	0.0 - 26.0
Time to meet decline criteria in IOL -n (%)	≤ 36 weeks	140 (50.0)	147 (51.2)	287 (50.6)
	> 36 weeks	140 (50.0)	140 (48.8)	280 (49.4)
Patient's living situation-n (%)				
	Living alone	29 (10.4)	32 (11.1)	61 (10.8)
	Living with caregiver or other	244 (87.1)	247 (86.1)	491 (86.6)
	Assisted living/ group home	7 (2.5)	8 (2.8)	15 (2.6)
Patients who met criteria of probable dementia with Lewy bodies - n (%)	Yes	6 (2.1)	8 (2.8)	14 (2.5)
	No	274 (97.9)	279 (97.2)	553 (97.5)
Previous AChEI use-n (%)	Yes	166 (59.3)	185 (64.5)	351 (61.9)
	No	114 (40.7)	102 (35.5)	216 (38.1)
Previous use of other approved AD treatments - n (%)	Yes	105 (37.5)	103 (35.9)	208 (36.7)
	No	175 (62.5)	184 (64.1)	359 (63.3)

AchEI - Acetycholinesterase inhibitor AD - Alzheimer's disease IOL - initial open-label phase

MMSE - Mini Mental State Examination

N is the number of patients in the Randomized population.
n is the number of patients meeting the criterion (for categorical variables); number of patients with a non-missing assessment (for continuous variables).

(a) Time since first symptom of AD is calculated with respect to IOL-baseline visit.
(b) MMSE at double-blind (DB) baseline.

Background characteristics at DB baseline which is the last assessment in the IOL phase are presented.

Source: PT-Table 14.1-3.3b

Source: Table 11-5 of sponsor's Clinical Study Report

3.2.1.6 Sponsor's Primary Efficacy Results

3.2.1.6.1 Cognition as Assessed by the ADAS-Cog

At the DB-baseline the ADAS-cog scores were comparable between the treatment groups, with the mean score at baseline of 34.4 and 34.9 in the Exelon 15 cm^2 and Exelon 10 cm^2 groups, respectively.

In the Exelon 15 cm^2 patch group, a slight numerical improvement in cognition was seen at DB-Week 12. Both treatment groups demonstrated cognitive decline from DB-baseline at DB-Week 24 and DB-Week 48 in the LOCF analysis. Patients treated with Exelon 15 cm^2 patch showed a numerically smaller decline in cognition from baseline at DB-Week 48 (primary endpoint); however the difference was not statistically significant (p-value=0.227). The results for the OC analysis were similar. Please refer to Table 5 for detailed results.

Table 5: Change from Baseline in ADAS-cog (ITT-DB Population)

Population	Visit		Exelon 15 cm^2 N = 265		Exelon 10 cm^2 N = 271		Exelon 15 cm^2 - Exelon 10 cm^2		
			n	Mean	n	Mean	DLSM	95% CI	p-value
LOCF		Baseline	264	34.4	268	34.9			
	DB-Week 12	Value	264	34.2	268	35.5			
		Change	264	-0.2	268	0.6	-0.9	(-2.0, 0.1)	0.091
	DB-Week 24	Value	264	35.4	268	37.1			
		Change	264	1.0	268	2.2	-1.3	(-2.5, -0.2)	0.027*
	DB-Week 48	Value	264	38.5	268	39.7			
		Change	264	4.1	268	4.9	-0.8	(-2.1, 0.5)	0.227
OC	DB-Week 12	Baseline	259	34.2	265	34.8			
		Value	259	34.0	265	35.5			
		Change	259	-0.2	265	0.6	-0.9	(-2.0, 0.2)	0.091
	DB-Week 24	Baseline	238	34.2	238	34.5			
		Value	238	35.1	238	36.7			
		Change	238	0.9	238	2.1	-1.3	(-2.5, -0.1)	0.035*
	DB-Week 48	Baseline	211	33.9	193	33.4			
		Value	211	38.2	193	38.7			
		Change	211	4.3	193	5.3	-1.2	(-2.7, 0.4)	0.141

ADAS-cog - Alzheimer's disease assessment scale-cognitive subscale
ANCOVA - analysis of covariance CI - confidence interval DB - double-blind
DLSM - difference in lease square means IOL - initial open-label

ADAS-cog scores range from 0 to 70, with lower scores indicating less severe impairment.
A negative difference in DLSM indicates greater improvement in Exelon 15 cm^2 as compared to Exelon 10 cm^2.

n is the number of patients with an assessment at baseline (last assessment in the IOL phase and either the corresponding visit (for the OC) or with at least 1 post baseline assessment (for the LOCF).

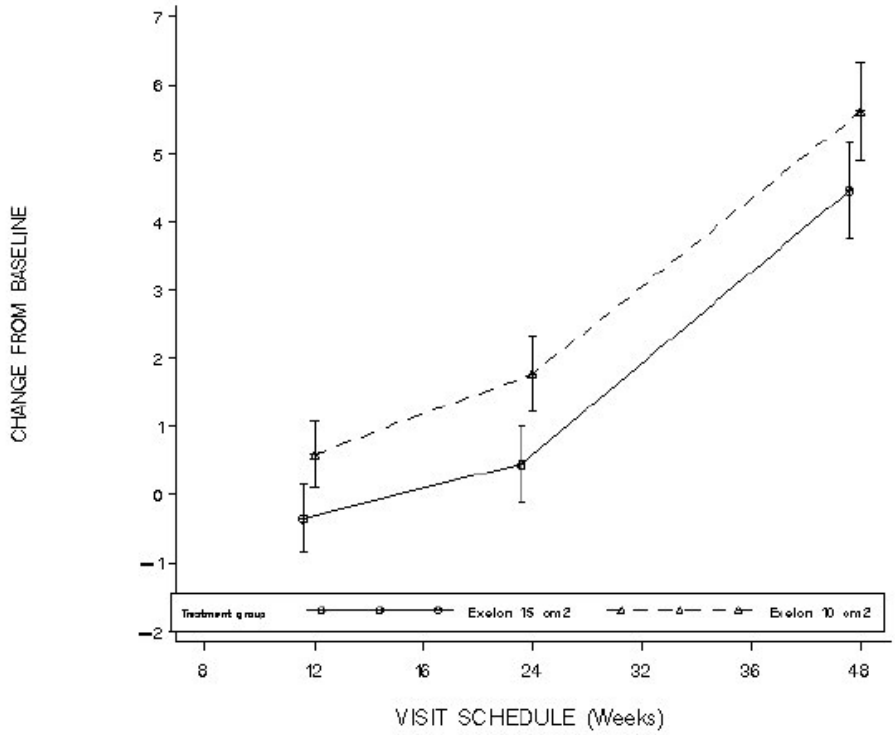
The DLSM, 95% CI, and p-value are based on an ANCOVA model adjusted for country and baseline ADAS-cog score.
* $p < 0.05$

Source: PT-Table 14.2-1.2

Source: Table 11-6 of sponsor's Clinical Study Report

The results are depicted graphically for the LOCF analysis (Figure 2).

Figure 2: ADAS-cog Change from Baseline (LSM(SEM), ITT-DB Population)



A negative change indicates an improvement from baseline.
Least square means (LSM) and the standard errors of the LSM (SEM) are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADAS-cog score.
$p < 0.05$ at double-blind Week 24 for Exelon 15 cm^2 patch vs. Exelon 10 cm^2 patch.
Source: PT-Figure 14.2-1.2a

Source: Figure 11-2 of sponsor's Clinical Study Report

3.2.1.6.2 Function as Assessed by ADCS-Instrumental ADL

At the DB-baseline the ADCS-Instrumental ADL scores were slightly higher in the Exelon 15 cm^2 patch compared to the Exelon 10 cm^2 patch (27.5 and 25.8, respectively).

Both treatment groups demonstrated functional decline from DB-baseline at 16, 24, 32, and 48 (primary endpoint) in the ITT-DB with LOCF analysis. Patients treated with the Exelon 15 cm^2 patch showed smaller decline (i.e. improved therapeutic benefit) in the instrumental activities of daily living as measured by the ADCS-Instrumental ADL subscale when compared to the lower dose treatment group, and the differences were statistically significant in favor of the Exelon 15 cm^2 patch from DB-Week 16 onwards. The results for the analysis of ITT-DB with LOCF are provided in Table 6.

Table 6: Change from Baseline in ADCS-Instrumental ADL (ITT-DB Population)

Population / Visit			Exelon 15 cm^2		Exelon 10 cm^2		Exelon 15 cm^2 - Exelon 10 cm^2		
			n	Mean	n	Mean	DLSM	95% CI	p-value
LOCF		Baseline	265	27.5	271	25.8			
	Week 8	Value	265	27.3	271	25.0			
		Change	265	-0.2	271	-0.8	0.8	(-0.2, 1.9)	0.114
	Week 12	Value	265	27.5	271	25.4			
		Change	265	0.1	271	-0.4	0.7	(-0.5, 1.8)	0.252
	Week 16	Value	265	26.7	271	24.0			
		Change	265	-0.7	271	-1.8	1.3	(0.2, 2.5)	0.025*
	Week 24	Value	265	26.0	271	22.9			
		Change	265	-1.5	271	-2.8	1.7	(0.5, 2.9)	0.005*
	Week 32	Value	265	25.2	271	21.7			
		Change	265	-2.2	271	-4.0	2.1	(0.9, 3.4)	<0.001*
	Week 48	Value	265	23.1	271	19.6			
		Change	265	-4.4	271	-6.2	2.2	(0.8, 3.6)	0.002*
OC	Week 8	Baseline	257	27.5	261	26.0			
		Value	257	27.3	261	25.2			
		Change	257	-0.2	261	-0.8	0.8	(-0.2, 1.9)	0.122
	Week 12	Baseline	250	27.5	259	25.8			
		Value	250	27.7	259	25.4			
		Change	250	0.3	259	-0.3	0.8	(-0.4, 2.0)	0.174
	Week 16	Baseline	237	27.3	243	26.2			
		Value	237	26.8	243	24.2			
		Change	237	-0.5	243	-2.0	1.7	(0.5, 2.9)	0.006*
	Week 24	Baseline	232	27.8	243	26.3			
		Value	232	26.8	243	23.3			
		Change	232	-1.0	243	-3.0	2.3	(1.0, 3.6)	<0.001*
	Week 32	Baseline	221	27.5	222	26.8			
		Value	221	25.6	222	22.6			
		Change	221	-1.9	222	-4.2	2.5	(1.1, 3.9)	<0.001*
	Week 48	Baseline	209	27.9	198	27.6			
		Value	209	23.3	198	20.7			
		Change	209	-4.6	198	-6.9	2.5	(0.8, 4.1)	0.004*

ADCS-Instrumental ADL - Alzheimer's disease cooperative study-Instrumental activities of daily living subscale
ANCOVA - analysis of covariance CI - confidence interval DLSM - difference in lease square means

ADCS-Instrumental ADL scores are caregiver-based, and range from 0 to 56, with higher scores indicating less severe impairment. A positive difference in DLSM indicates greater improvement in Exelon 15 cm^2 as compared to Exelon 10 cm^2.

n is the number of patients with an assessment at baseline (last assessment in the initial open-label phase) and either the corresponding visit (for the OC) or with at least 1 post baseline assessment (for the LOCF).

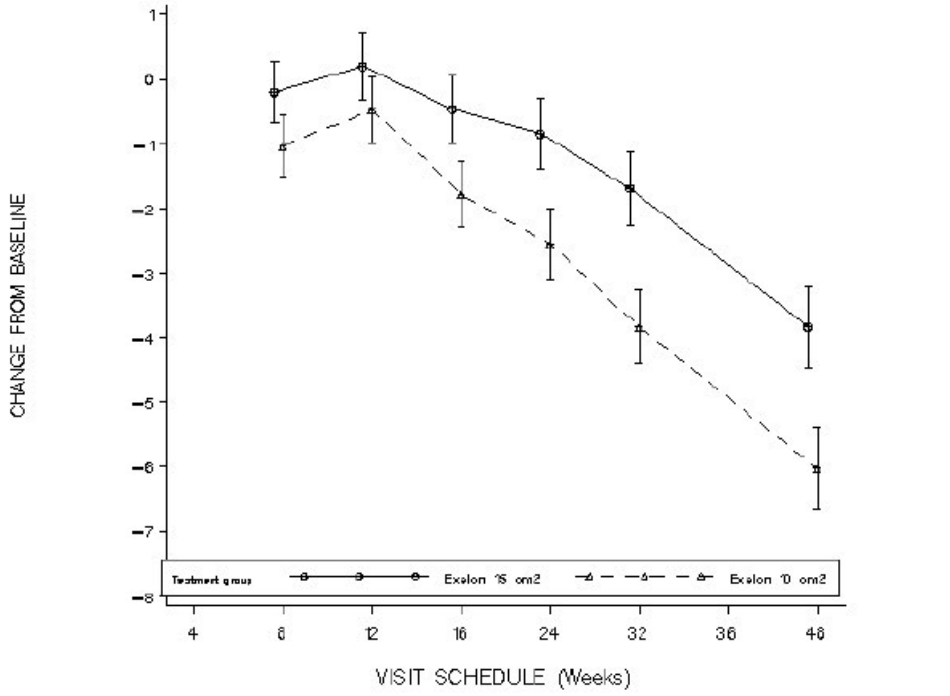
The DLSM, 95% CI, and p-value are based on an ANCOVA model adjusted for country and baseline ADCS-Instrumental ADL score.

Source: PT-Table 14.2-2.2

Source: Table 11-7 of sponsor's Clinical Study Report

The results are depicted graphically for the LOCF analysis (Figure 3).

Figure 3: ADCS-Instrumental ADL Change from Baseline (LSM(SEM), ITT-DB Population)



A positive change indicates an improvement from baseline.

Least square means (LSM) and the standard errors of the LSM (SEM) are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline ADCS-Instrumental ADL score.
$p < 0.05$ at double-blind Weeks 16, 24, 32, and 48 for Exelon 15 cm^2 patch vs. Exelon 10 cm^2 patch.

Source: PT-Figure 14.2-2.1a

Source: Figure 11-3 of sponsor's Clinical Study Report

3.2.1.7 Sponsor's Sensitivity Analyses for Co-primary Endpoints

For both co-primary endpoints, comparison of the treatments was also performed on the ITT-DB with LOCF via the non-parametric van Elteren test stratified by country as a supportive analysis.

Sensitivity analyses were performed on the ITT-DB population with OC for both co-primary variables based on a mixed-effects repeated measures model (MMRM). The model included fixed effects for treatment group, country, baseline score, visit and treatment group-by-visit interaction and random effect for subject.

The results of these sensitivity analyses were consistent with those of the primary efficacy analyses.

Reviewer's Comments: For this study, LOCF was used to handle missing data in the primary efficacy analyses, which was previously agreed between the sponsor and the Agency at the study design stage. According to a recent publication, "*The prevention and treatment of missing data in clinical trials*" by the National Academies, LOCF as primary efficacy analysis is discouraged. However, for this particular study, since the results of LOCF analysis are consistent with those of

various sensitivity analyses, using LOCF in the primary efficacy analyses doesn't affect the interpretation of the efficacy results.

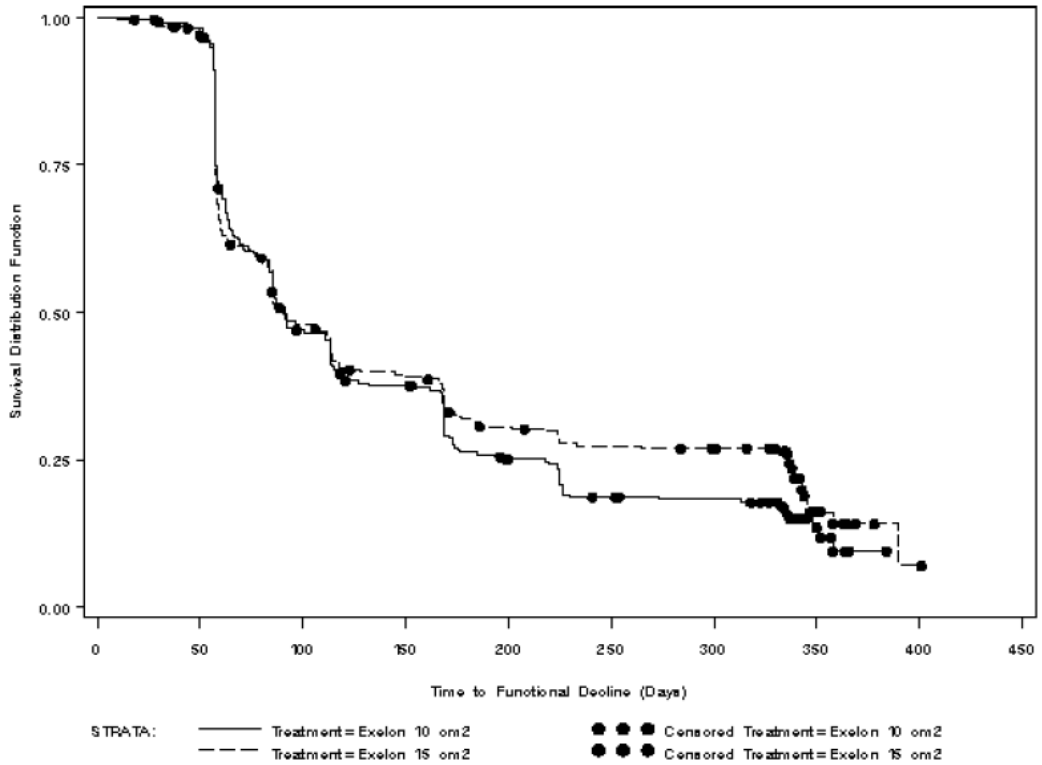
3.2.1.8 Sponsor's Secondary Efficacy Results

3.2.1.8.1 Time to Functional Decline Measured by ADCS-Instrumental ADL in the DB Phase

In the DB phase, functional decline was defined by either an at least 1 point decrease in the ADCS-Instrumental ADL score in a visit and confirmed by the following visit/assessment or at least 2 points decrease from DB randomization baseline, and still at least 1 point less at the subsequent confirmation visit. The analysis was carried out for the ITT-DB and the PP-DB populations with OC.

For the ITT-DB population with OC dataset, the Exelon 15 cm^2 patch group showed a slower decrease in function from baseline than the Exelon 10 cm^2 patch group, as assessed by the ADCS-Instrumental ADL score (Figure 4). However, the nominal p-value of the log-rank test for treatment comparison was not significant (p=0.186). Similar results were shown for the PP-DB population with OC (p=0.061).

Figure 4: Time to Functional Decline in ADCS-Instrumental ADL (ITT-DB)



Source: Figure 11-5 of sponsor's Clinical Study Report

3.2.1.8.2 Attention and Executive Function as Assessed by the Trail Making Test (Parts A and B) in the DB Phase

At DB-baseline the mean time for both TMT Parts A and B were slightly longer in the Exelon 10 cm^2 when compared to the Exelon 15 cm^2 group. The Exelon 15 cm^2 group had numerically smaller increases in time to complete the TMT Part A at DB-Weeks 24 and 48 as compared to the Exelon 10 cm^2 patch, with the greatest difference seen at DB-Week 24; however, the nominal p-values for the differences in LSM were not statistically significant for the LOCF or OC results. The Exelon 15 cm^2 group had numerically higher increases in time to complete the TMT Part B at DB-Weeks 24 and 48 compared to the Exelon 10 cm2 patch. The greatest LSM difference seen at DB-Week 24; however, the between treatment group LSM differences were not statistically significant for the LOCF or OC results at any time point (Table 7).

Table 7: Change from Baseline in Trail Making Test (TMT) Part A and B (ITT-DB)

Population / Visit		Exelon 15 cm^2		Exelon 10 cm^2		Exelon 15 cm^2 - Exelon 10 cm^2		
		n	Mean	n	Mean	DLSM	95% CI	p-value
Trail making test (TMT) - Part A								
LOCF	Baseline	254	191.3	258	199.4			
Week 24	Post-baseline	254	195.6	258	209.6			
	Change	254	4.2	258	10.2	-7.8	(-17.3, 1.7)	0.105
Week 48	Post-baseline	254	207.6	258	217.6			
	Change	254	16.3	258	18.2	-3.8	(-14.3, 6.6)	0.473
OC	Baseline	214	177.2	204	186.2			
Week 24	Post-baseline	214	182.3	204	199.1			
	Change	214	5.0	204	12.9	-10.6	(-22.1, 1.0)	0.072
Week 48	Baseline	163	172.4	142	169.2			
	Post-baseline	163	195.0	142	192.8			
	Change	163	22.6	142	23.5	-0.9	(-15.9, 14.1)	0.905
Trail making test (TMT) - Part B								
LOCF	Baseline	235	372.2	236	380.8			
Week 24	Post-baseline	235	377.7	236	381.6			
	Change	235	5.5	236	0.9	1.6	(-9.9, 13.1)	0.784
Week 48	Post-baseline	235	381.4	236	386.6			
	Change	235	9.3	236	5.8	0.8	(-10.1, 11.8)	0.881
OC	Baseline	189	364.7	178	370.9			
Week 24	Post-baseline	189	371.5	178	372.1			
	Change	189	6.9	178	1.2	2.8	(-11.8, 17.5)	0.704
Week 48	Baseline	139	360.9	120	366.2			
	Post-baseline	139	370.5	120	371.0			
	Change	139	9.6	120	4.8	1.7	(-15.6, 18.9)	0.850

The baseline assessment corresponds to the last assessment in the initial open-label (IOL) phase.

A negative change indicates an improvement from baseline. A negative difference (DLSM) indicates greater improvement in Exelon 15cm² as compared to Exelon 10cm².

Difference of least square means (DLSM), 95% confidence interval (CI), and p-value are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline TMT score.

* $p < 0.05$

n is the number of patients with an assessment at baseline and the corresponding visit (OC) and at least 1 post-baseline assessment (LOCF).

Source: PT-Table 14.2-3.2

Source: Table 11-8 of sponsor's Clinical Study Report

3.2.1.8.3 Neuropsychiatric Inventory (NPI) in the DB Phase

For both the LOCF and OC analyses of the ITT-DB population, both treatment groups showed slight deterioration or no change from baseline at endpoint in both the NPI-10 and NPI-D scales. Based on nominal p-values, the between dose treatment group were not statistically significant (Table 8).

Table 8: Change from Baseline in Neuropsychiatric Inventory (NPI) Score (ITT-DB)

Population / Visit		Exelon 15 cm^2 n	Exelon 15 cm^2 Mean	Exelon 10 cm^2 n	Exelon 10 cm^2 Mean	Exelon 15 cm^2 - Exelon 10 cm^2 DLSM	95% CI	p-value
Neuropsychiatric Inventory (NPI) 10 - Total Score								
LOCF	Baseline	265	12.4	271	14.4			
DB endpoint	Post-baseline	265	13.8	271	15.4			
	Change	265	1.4	271	0.9	-0.1	(-1.9, 1.7)	0.927
OC	Baseline	243	11.8	241	13.7			
DB endpoint	Post-baseline	243	13.3	241	14.7			
	Change	243	1.5	241	1.1	-0.1	(-2.1, 1.9)	0.899
NPI-D: Distress score								
LOCF	Baseline	265	6.5	271	8.1			
endpoint	Post-baseline	265	7.1	271	8.1			
	Change	265	0.6	271	-0.0	0.2	(-0.7, 1.2)	0.647
OC	Baseline	243	6.1	241	7.7			
DB endpoint	Post-baseline	243	6.8	241	7.7			
	Change	243	0.7	241	-0.0	0.2	(-0.8, 1.2)	0.707

DB-endpoint is the last assessment during double-blind phase.

A negative change indicates an improvement from baseline. A negative difference (DLSM) indicates greater improvement in Exelon 15cm^2 as compared to Exelon 10cm^2.

Difference of least square means (DLSM), 95% confidence interval (CI), and p-value are based on an analysis of covariance (ANCOVA) model adjusted for country and baseline NPI score.

* $p < 0.05$

n is the number of patients with an assessment at baseline and DB-endpoint.

Source: PT-Table 14.2-4.2

Source: Table 11-9 of sponsor's Clinical Study Report

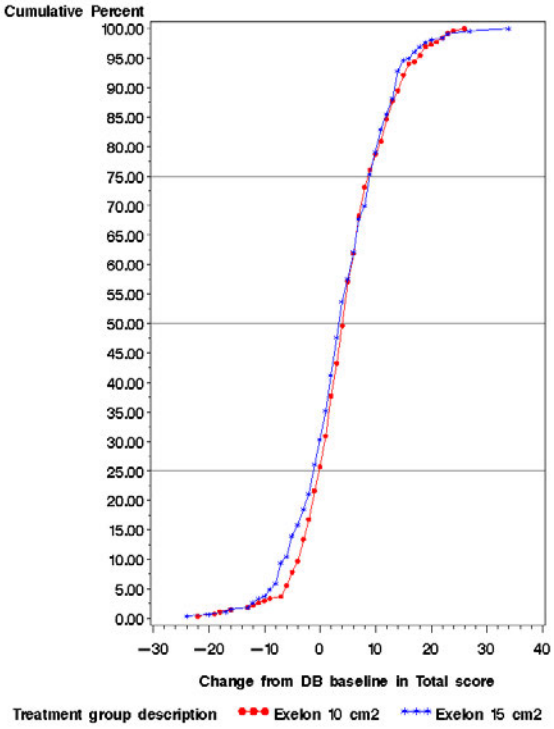
3.2.2 REVIEWER'S ANALYSIS

This reviewer verified sponsor's efficacy analyses presented in this review. The analyses in this section were conducted by this reviewer.

3.2.2.1 CDF for Co-primary Endpoints

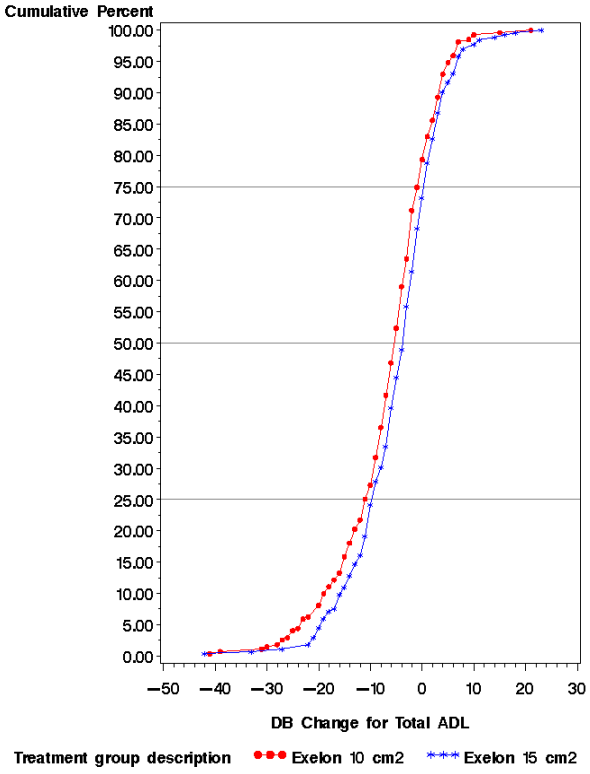
The Cumulative Distribution Function (CDF) for the co-primary endpoints, change from baseline in ADAS-cog and ADCS-Instrumental ADL at Week 48, is presented in Figure 5 and Figure 6. For ADAS-cog (lower scores indicating less severe impairment), the two CDFs are generally very close to each other, which shows that the treatment difference between the two groups is small. For ADCS-ADL (higher scores indicating less severe impairment), it seems that the CDF for Exelon 10 cm^2 group is generally slightly above the CDF for Exelon 15 cm^2 group, indicating that the patients in Exelon 15 cm^2 group had smaller decline in ADCS-Instrumental ADL score than those in Exelon 10 cm^2 group.

Figure 5: CDF for ADAS-cog (ITT-DB)



Source: Reviewer's Analysis

Figure 6: CDF for ADCS-Instrumental ADL (ITT-DB)



Source: Reviewer's Analysis

3.2.2.2 Treatment Effect by Country

This study was conducted in seven countries with approximately 40% of the randomized patients from United States. Table 9 and Table 10 present the change from baseline and treatment effect at Week 48 for ADAS-cog and ADCS-Instrumental ADL, respectively. The treatment effect is defined as the difference between the mean change from baseline of Exelon 15 cm^2 and mean change from baseline of Exelon 10 cm^2.

Table 9: Change from Baseline and Treatment Effect at Week 48 in ADAS-cog (ITT-DB)

Country	Treatment Group	N	Mean	Std Dev	Treatment Effect	Standard Error
CAN	Exelon 10 cm2	36	5.47	6.28	0.23	1.59
	Exelon 15 cm2	30	5.70	6.62		
CHE	Exelon 10 cm2	6	2.17	3.54	6.26	2.49
	Exelon 15 cm2	7	8.43	5.13		
DEU	Exelon 10 cm2	39	5.62	9.98	-4.52	2.24
	Exelon 15 cm2	31	1.10	8.34		
ESP	Exelon 10 cm2	9	2.89	7.87	-4.27	3.47
	Exelon 15 cm2	8	-1.38	6.19		
FRA	Exelon 10 cm2	23	6.00	6.51	2.15	2.50
	Exelon 15 cm2	27	8.15	10.36		
ITA	Exelon 10 cm2	54	3.19	6.38	0.60	1.31
	Exelon 15 cm2	57	3.79	7.34		
USA	Exelon 10 cm2	101	5.31	7.65	-1.47	1.07
	Exelon 15 cm2	104	3.84	7.68		

Source: Reviewer's Analysis

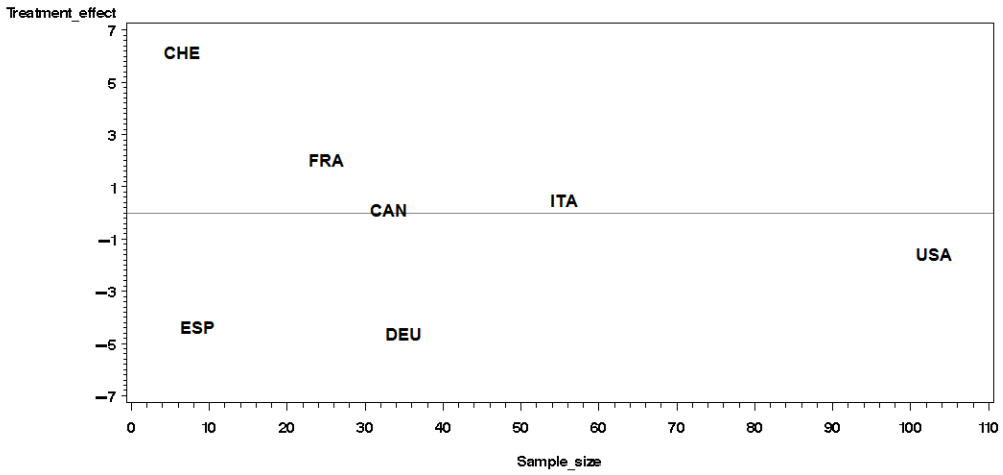
Table 10: Change from Baseline and Treatment Effect at Week 48 in ADCS-Instrumental ADL (ITT-DB)

Country	Treatment Group	N	Mean	Std Dev	Treatment Effect	Standard Error
CAN	Exelon 10 cm2	36	-4.00	6.12	-2.03	1.75
	Exelon 15 cm2	30	-6.03	8.08		
CHE	Exelon 10 cm2	6	-10.17	8.68	3.17	4.05
	Exelon 15 cm2	7	-7.00	5.86		
DEU	Exelon 10 cm2	40	-6.78	10.27	3.21	2.05
	Exelon 15 cm2	32	-3.56	6.01		
ESP	Exelon 10 cm2	9	-2.33	8.92	2.96	3.26
	Exelon 15 cm2	8	0.63	2.33		
FRA	Exelon 10 cm2	23	-6.61	9.89	1.24	2.54
	Exelon 15 cm2	27	-5.37	8.10		
ITA	Exelon 10 cm2	55	-5.33	7.48	0.19	1.53
	Exelon 15 cm2	57	-5.14	8.60		
USA	Exelon 10 cm2	102	-7.13	9.26	3.48	
	Exelon 15 cm2	104	-3.64	8.94		

Source: Reviewer's Analysis

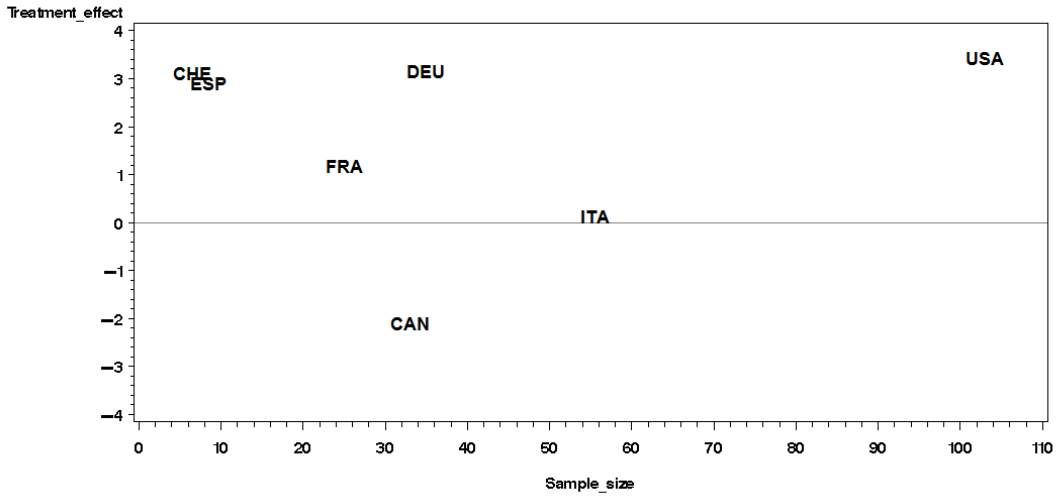
Figure 7 and Figure 8 present treatment effect versus average sample size of treatment groups by country.

Figure 7: Treatment Effect versus Average Sample Size by Country for ADAS-cog (ITT-DB)



Source: Reviewer's Analysis

Figure 8: Treatment Effect versus Average Sample Size by Country for ADCS-Instrumental ADL (ITT-DB)



Source: Reviewer's Analysis

For ADAS-cog, the point estimates of treatment effect are in the same direction as the overall patients for United States (USA), Germany (DEU), and Spain (ESP). In this study, fifty-four percent (54%) of the patients were randomized in these three countries. In the contrast, for Canada (CAN), France (FRA), Switzerland (CHE), and Italy (ITA), the mean change from

baseline in ADAS-cog at Week 48 for Exelon 15 cm^2 group was numerically larger than that for Exelon 10 cm^2 group. The difference in the treatment effect among countries isn't surprising as the p-value for this co-primary endpoint didn't reach statistical significance (p=0.227). For ADCS-Instrumental ADL, the point estimates of treatment effect are in the same direction as the overall patients except for Canada.

The US ITT-DB population represents 38% of the total ITT-DB population (N=206/536). For US ITT-DB population only, based on the pre-specified primary efficacy analyses, the p-value for ADAS-cog was 0.1706 and the p-value for ADCS-Instrumental ADL was 0.0017.

3.3 Evaluation of Safety

Please read Dr. Kozauer's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Geographic Region

4.1.1 STUDY ENA713D2340

4.1.1.1 Gender, Race and Age

The co-primary endpoints ADAS-cog and ADCS-Instrumental ADL are summarized by subgroups and treatments in Table 11.

It seems that that the point estimates of treatment effect are in the same direction as the overall patients across the patient subgroups investigated, except that the mean change from baseline in ADAS-cog for males was numerically slightly lower in the Exelon 10 cm^2 group than that in Exelon 15 cm^2 group and the mean change from baseline in ADCS-Instrumental ADL for non-Caucasians was numerically higher in in the Exelon 10 cm^2 group than that in Exelon 15 cm^2 group.

Table 11: Subgroup Analysis by Gender, Race and Age (ITT-DB, LOCF)

Endpoints and Subgroups	Exelon 15 cm^2 N=265			Exelon 10 cm^2 N=271		
	N	Mean	STD	N	Mean	STD
Change from Baseline in ADAS-cog at Week 48						
Female	173	3.77	7.88	171	5.08	7.38
Male	91	4.78	8.24	97	4.46	7.70
Caucasian	251	4.10	7.96	263	4.83	7.54
Non-Caucasian	13	4.46	9.13	5	6.40	4.28
<65 Years Old	31	4.00	7.92	17	6.41	7.47
>=65 Years Old	233	4.14	8.03	251	4.75	7.49
Change from Baseline in ADCS-Instrumental ADL at Week 48						
Female	174	-4.04	8.12	173	-6.56	9.22
Male	91	-4.98	8.39	98	-5.45	7.94
Caucasian	252	-4.44	8.06	266	-6.30	8.79
Non-Caucasian	13	-2.85	11.08	5	1.20	3.56
<65 Years Old	31	-3.10	7.54	17	-8.00	8.48
>=65 Years Old	234	-4.53	8.30	254	-6.04	8.80

Source: Reviewer's Analysis

4.1.1.2 Geographic Region

Please refer to Section 3.2.2.2 for treatment effect by country.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study D2340 was a prospective, multicenter, randomized, double-blind (DB), double-dummy, parallel group study in patients with mild to moderate dementia of the Alzheimer's type. The study was designed to compare the efficacy and safety of treatment with Exelon 15 cm2 patch to Exelon 10 cm2 patch during a 48 week DB treatment phase in patients who demonstrated functional and cognitive decline after 24 to 48 weeks of treatment with Exelon 10 cm2 patch during an Initial Open Label (IOL) period. This study was conducted in Canada, France, Germany, Italy, Spain, Switzerland, and the United States.

The study consisted of the following phases: Screening phase (up to 5 weeks), IOL phase (24-to 48 weeks), DB phase (48 weeks), and Extended open-label (EOL) phase (48 weeks). There were 1979 patients screened for this study. A total of 1582 patients were enrolled into the IOL phase and exposed to study drug. At the end of the IOL phase, 567 patients were classified as decliners and randomized into the DB phase. Of the 567 randomized patients, 410 patients (72.3%) completed the study. The study completion rates were similar between the treatment groups, 70.7% for Exelon 10 cm2 group and 73.9% for Exelon 15 cm2 group.

The co-primary efficacy analysis variables were the change from DB randomization baseline to DB Week 48 in the ADAS-cog total score and ADCS-Instrumental ADL score. Both co-primary outcome variables were analyzed using Analysis of Covariance (ANCOVA) model adjusted for country and baseline score. The primary analysis was based on the ITT-DB population using last observation carried forward (LOCF) to account for missing values. The p-value for ADAS-cog was 0.227 and the p-value for ADCS-Instrumental ADL was 0.002. The results of various sensitivity analyses, including non-parametric analysis and MMRM analysis, were consistent with those of the pre-specified primary efficacy analyses. The nominal p-values for the three secondary efficacy variables were not statistically significant. Please refer to Section 3.2.1 for details.

For this study, LOCF was used to handle missing data in the primary efficacy analyses, which was previously agreed between the sponsor and the Agency at the study design stage. According to a recent publication, "The prevention and treatment of missing data in clinical trials" by the National Academies, LOCF as primary efficacy analysis is discouraged. However, for this particular study, since the results of LOCF analysis are consistent with those of various sensitivity analyses, using LOCF in the primary efficacy analyses doesn't affect the interpretation of the efficacy results.

Treatment effect was further analyzed by country. The treatment effect was defined as the difference between the mean change from baseline of Exelon 15 cm2 and mean change from baseline of Exelon 10 cm2. For ADAS-cog, the point estimates of treatment effect were in the same direction as the overall patients for United States, Germany, and Spain. In this study, fifty-four percent (54%) of the patients were randomized in these three countries. In contrast, for Canada, France, Switzerland, and Italy, the mean change from baseline in ADAS-cog at Week 48 for Exelon 15 cm2 group was numerically larger than that for Exelon 10 cm2 group. The

difference in the treatment effect among countries isn't surprising as the p-value for this co-primary endpoint didn't reach statistical significance (p=0.227). For ADCS-Instrumental ADL, the point estimates of treatment effect were in the same direction as the overall patients except for Canada. The US ITT-DB population represents 38% of the total ITT-DB population (N=206/536). For US ITT-DB population only, based on the pre-specified primary efficacy analyses, the p-value for ADAS-cog was 0.1706 and the p-value for ADCS-Instrumental ADL was 0.0017. Please refer to Section 3.2.2.2 for detailed analyses.

5.2 Conclusions and Recommendations

This submission includes a single phase III pivotal efficacy study CENA713D2340 (Study D2340). Based on the results of Study D2340, the trial demonstrated a statistically significant effect on ADCS-Instrumental ADL (the co-primary global endpoint, p=0.002); however, the treatment difference on ADAS-cog (the co-primary cognitive endpoint) was not statistically significant (p=0.227). Since for Alzheimer's Disease the trial usually needs to win on both cognitive and global endpoints for an efficacy claim, there is no sufficient statistical evidence to support the efficacy of Exelon 15 cm2 patch in the treatment of mild to moderate Alzheimer's Disease, compared to Exelon 10 cm2 patch.

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/s/

JINGYU J LUAN
07/25/2012

KUN JIN
07/25/2012
I concur with the review.

HSIEN MING J HUNG
07/26/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDQA (Biopharmaceutics) Review

NDA	22-083 (S046)
Applicant:	Novartis Pharmaceuticals
Tradename:	Exelon® Patch
Stamp Dates	10/28/2011
Established Name:	Rivastigmine
Dosage Form:	Transdermal System
Route of Administration:	Topical
Strength(s), and Dosing Regimen:	13.3 mg/24 hours (27 mg, 15cm^2)
Indication:	Treatment of mild to moderate Alzheimer's disease
OND Division:	Division of Neurologic Products
Reviewer	Tapash Ghosh, PhD

SUMMARY

Background: The once-daily Exelon transdermal patch was approved in the United States on 7/6/2007 under NDA 22-083 for the treatment of mild to moderate dementia of the Alzheimer's type and for the treatment of mild to moderate dementia associated with Parkinson's disease. The currently approved Exelon patches are available in 2 sizes, a 5 cm^2 patch and a 10 cm^2 patch.

The original NDA covers (b) (4) strengths (9 mg/5 cm^2, 18 mg/10 cm^2, (b)). However, (b) (4) strengths (9 mg/5 cm^2, 18 mg/10 cm^2) were approved (b) (4). Following approval of these two strengths, a number of CMC changes for the drug product have been approved, including an alternate drug product (DP) manufacturing site at LTS Lohmann Therapy Systems Corp, West Caldwell NJ for these two strengths (9 mg/5 cm^2, 18 mg/10 cm^2).

Current Submission: In this supplement, the Applicant is seeking approval of the Exelon 27mg/15 cm^2 (rivastigmine) transdermal system (13.3 mg/24 hours) in patients with mild to moderate Alzheimer's disease. An efficacy and safety study (Study D2340) was conducted to support the approval of the 27mg/15 cm^2 patch.

The CMC information submitted in this efficacy supplement for the new dosing strength of the Exelon Patch is essentially the same as that provided in the original NDA submission. Note that although (b) (4) the CMC Reviewer recommended approval with (b) (4) expiry.

The drug product description of manufacturing process and process control is identical to the approved manufacturing process and process controls for the 9 mg/5cm^2 and 18 mg/10 cm^2 strengths. In essence, this new strength will be (b) (4) the size of the patch (See CMC reviews for the specific details).

Review: This Biopharmaceutics review is focused on the evaluation and acceptability of the comparative *in vitro* release profile and similarity f2 data supporting the approval of the alternate manufacturing site at LTS Lohmann Therapy Systems Corp, West Caldwell NJ in addition to Lohmann Therapie Systeme AG manufacturing facility in Andernach, Germany. Note that the patches used in the clinical Study D2340 as well as the patches used to generate the PK information (b) (4) were manufactured at Lohmann Therapie Systeme AG manufacturing facility in Andernach, Germany.

Recommendation:

Based on similarity of dissolution profiles of (b) (4) transdermal patches manufactured at two different facilities using the approved dissolution method, both facilities (West Caldwell, NJ and Andernach, Germany) are recommended for approval as DP manufacturing sites for the proposed 27mg/15cm^2 Exelon® transdermal patches.

Tapash K. Ghosh, Ph. D.
Primary Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Richard T. Lostritto, Ph. D.
Acting Biopharmaceutics Supervisor
Office of New Drug Quality Assessment

BIOPHARMACEUTICS ASSESSMENT

Supportive Dissolution Data

A dissolution profile comparison was made between two batches of ENA713 27mg/15cm^2 transdermal patches sourced from the two different manufacturers using the following approved dissolution method:

Apparatus:	USP Apparatus 6 (cylinder)
Medium:	0.9% Sodium Chloride solution
Temperature:	32ºC ± 0.5 ºC
Speed:	50 rpm

The analysis was run on 12 units of each of the following batches: batch 7023121G manufactured at LTS AG (Andernach, Germany) and batch 990118-8 manufactured at LTS Corp (West Caldwell, USA).

The difference factor (f1) and the similarity factor (f2) were calculated based on the dissolution measurements performed at 5 time points, respectively after 0, 0.5, 2, 4, 7 hours. The results are tabulated in Table 3-3. As Figure 3-1 shows, the two batches have similar dissolution profiles.

Table 3-1 **ENA713 27mg/15cm^2 Transdermal therapeutic system: Dissolution results for batch 7023121G, manufactured at LTS AG (Andernach, Germany)**

Unit number	% dissolved at t hours			
	0.5 h	2 h	4 h	7 h
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	31.42	61.25	72.75	79.50
SD	1.64	1.23	1.04	1.14

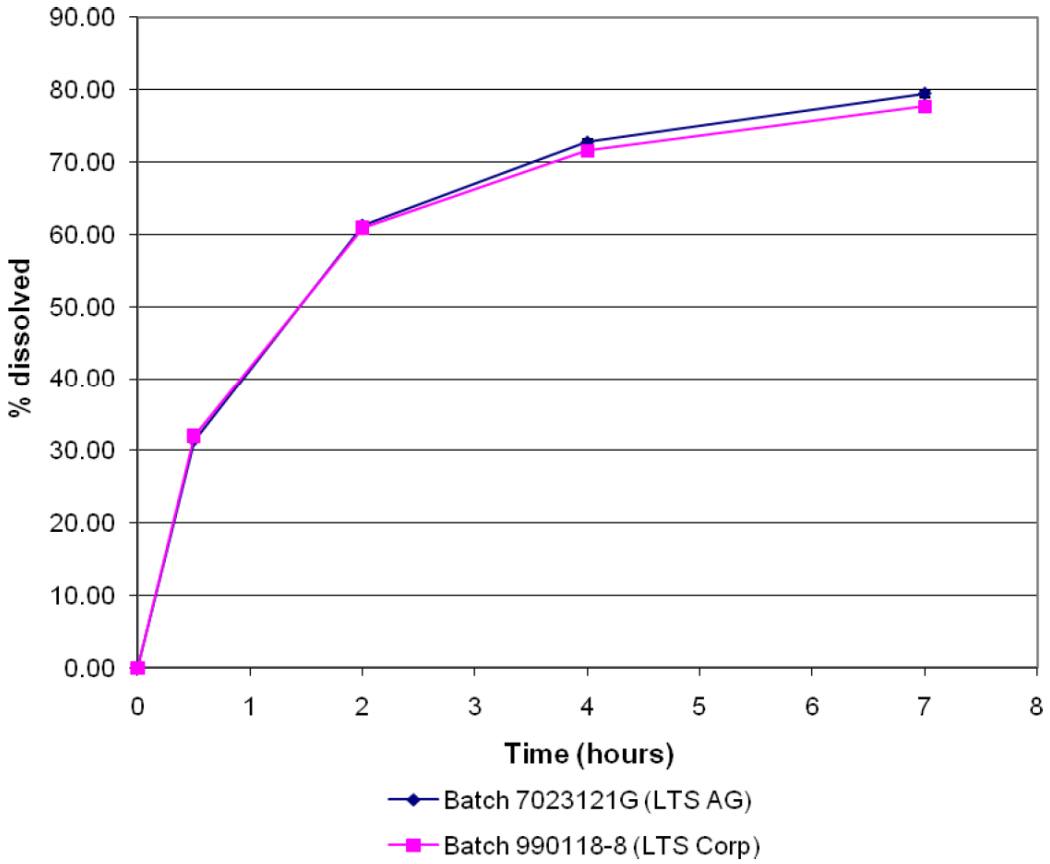
Table 3-2 **ENA713 27mg/15cm^2 Transdermal therapeutic system: Dissolution results for batch 990118-8, manufactured at LTS Corp (West Caldwell, USA)**

Unit number	% dissolved at t hours			
	0.5 h	2 h	4 h	7 h
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	32.00	60.92	71.58	77.67
SD	2.31	1.48	1.73	1.85

Table 3-3 **Calculation of difference factor (f_1) and similarity factor (f_2)**

Time (hours)	Mean data				|Rt-Tt|	|Rt-Tt|^2
	Rt	CV	Tt	CV		
0.5	31.42	1.64	32.00	2.31	0.58	0.34
2	61.25	1.23	60.92	1.48	0.33	0.11
4	72.75	1.04	71.58	1.73	1.17	1.36
7	79.50	1.14	77.67	1.85	1.83	3.36
Σ Rt		**ΣTt**			**Σ|Rt-Tt|**	**Σ|Rt-Tt|^2**
244.92		242.17			3.92	5.17
Parameter		**Result**			**Criteria**	**Description**
f_1		1.60			0-15	Similar
f_2		92.29			50-100	Similar

Figure 3-1 Dissolution profiles



Reviewer's Comments: *Based on similarity of dissolution profiles of 27mg/15cm^2 transdermal patches manufactured at two different facilities using the approved dissolution method, both facilities (*LTS Lohmann Therapy Systems Corp, West Caldwell in NJ and Lohmann Therapie Systeme AG manufacturing facility in Andernach, Germany) *are recommended for approval as DP manufacturing sites for the proposed 27mg/15cm^2 transdermal patches. Of note, for the approved strengths 9 mg/5 cm^2, 18 mg/10 cm^2, these two facilities are already approved.*

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/s/

TAPASH K GHOSH
08/30/2012

RICHARD T LOSTRITTO
08/30/2012

Clinical Pharmacology Review

PRODUCT (Generic Name):	Rivastigmine
NDAs:	22-083/S0046
PRODUCT (Brand Name):	EXELON PATCH
DOSAGE FORM:	Transdermal Patch
DOSAGE STRENGTH:	15 cm^2 (13.3 mg/24hrs)
INDICATION:	Treatment of dementia of Alzheimer's type (AD) and Parkinson's type (PDD)
NDA TYPE:	NDA Supplement
SUBMISSION DATE:	10/31/2011
SPONSOR:	Novartis
REVIEWER:	Jagan Mohan Parepally, Ph.D.
TEAM LEADER:	Angela Men, M.D., Ph.D.
OCP DIVISION:	DCP 1
OND DIVISION:	HFD 120

TABLE OF CONTENTS

I. EXECUTIVE SUMMARY

Rivastigmine (ENA713, Exelon®) is a slowly reversible (pseudo-irreversible), brain selective, dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) of the carbamate type. Two rivastigmine oral formulations are approved and marketed worldwide, Exelon® capsule and the bioequivalent oral solution. Also, two strengths/sizes of Exelon® patch, 9 mg/5 cm^2 and 18 mg/10 cm^2 were approved for marketing. The current submission is a supplemental New Drug Application for NDA 22-083 Exelon® Patch (rivastigmine transdermal system) seeking approval of a new dosage strength of the transdermal formulation (13.3 mg/24 hours nominal release rate, 27 mg total drug load, 15cm^2 patch size) for use in the currently approved indications for the treatment of mild to moderate dementia of the Alzheimer's type (AD) and for the treatment of mild to moderate dementia associated with Parkinson's disease (PDD).

The sponsor conducted a pivotal trial CENA713D2340 (Study D2340) with the intent to seek approval of the Exelon 15 cm^2 patch (13.3 mg/24 hours) in patients with mild to moderate Alzheimer's disease. Study D2340 was a 48-week, multicenter, randomized, double-blind, parallel group trial, which evaluated the comparative efficacy, safety and tolerability of Exelon® 10 cm^2 and 15 cm^2 patch in patients with AD.

The clinical pharmacology program outlined in the original submission of Exelon® transdermal patch submitted in 2006 included the clinical pharmacology characterization (b) (4) (b) (4) An in vitro study to evaluate rivastgmine's potential to inhibit CYP2B6 was conducted per Office of Clinical Pharmacology's recommendation. The original submission is referred in the current application for the pharmacokinetics of 15 cm^2 (13.3 mg/24 h) dosage strength of Exelon® transdermal Patch.

II. RECOMMENDATION

The Office of Clinical Pharmacology/Division of Clinical Pharmacology I (OCP/DCP-1) has reviewed sNDA #22-083 including an in vitro study to evaluate rivastgmine's potential to inhibit CYP2B6. No new clinical pharmacology studies were conducted with the Exelon® transdermal patch strength 15 cm^2 for this submission.

III. LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling. The proposed changes are acceptable.

(b) (4)

(b) (4)

IV. Summary of Clinical Pharmacology and Biopharmaceutics

Followings are some of the highlights of Clinical Pharmacology and Biopharmaceutics information for Exelon® transdermal patch strength 15 cm^2. For detailed information, please refer to the Clinical Pharmacology review of the original application reviewed by Dr. Tandon (DARRTS 6/15/2007).

General Pharmacokinetics (ADME characteristics):

Absorption: Absorption of rivastigmine from the patch was slow with a lag time of approximately 0.5 - 1 h after the first application. Concentrations subsequently increased slowly, typically reaching a plateau close to maximum at approximately 8 h, although

Tmax typically occurred between 8-26 hours, with mean usually around 14-16 hours across studies.

Distribution: Rivastigmine is weakly (approximately 40%) bound to plasma proteins.

Metabolism: Rivastigmine is rapidly and extensively metabolized, primarily via esterase-mediated hydrolysis of the carbamate moiety to the phenolic metabolite NAP226-90 and its sulfate conjugate following oral administration to animals and man. NAP226-90 is considered to be pharmacologically inactive. Rivastigmine has a low affinity for cytochrome P450 enzymes. Lower metabolite-to-parent AUC_{24h} ratio (3 to 5-fold) was observed after dermal compared to oral administration, indicating that much less metabolism occurred after dermal compared to the oral treatment. There were no indications of dermal metabolism either.

Elimination: Major pathway of elimination is via the kidneys. Rivastigmine was mainly excreted in urine as the sulfate conjugate of NAP226-90 (renal clearance was 13 – 25 L/h, CV = 19-37%). Approximately 3% of the rivastigmine dose was excreted unchanged in urine following patch, administration.
The plasma elimination half-life ($t_{1/2}$) of rivastigmine after multiple 24-hour 20 cm^2 patch applications in AD patients was 3.4 ± 0.7 h (CV = 22%).

Single dose and multiple dose pharmacokinetics:
The pharmacokinetics of rivastigmine was time in variant. Steady-state plasma concentrations of rivastigmine were achieved at the second day of dosing dose level in accordance with the short half-life of rivastigmine. The accumulation factor was 1.3 for the Exelon 15 cm^2 patch.

Dose proportionality: Rivastigmine exhibits nonlinear pharmacokinetics following both oral and intravenous administrations because of capacity-limited elimination. The patch formulation also displays nonlinear rivastigmine pharmacokinetics which, however, was less pronounced than with the oral formulation.

Pharmacokinetics in patients: The pharmacokinetics of rivastigmine and NAP226-90 are similar in the AD patients and healthy volunteers when given the same patch size applied to the same body site.

Special Populations:

Renal Impairment: No new studies have been conducted with Exelon patches in subjects with renal impairment. Based on population analysis creatinine clearance did not show any clear effect on rivastigmine steady state concentrations
Hepatic Impairment: No new studies have been conducted with Exelon patches in subjects with hepatic impairment. Based on population analysis SGOT and SGPT did not show any clear effect on rivastigmine steady state concentrations (p=0.12 and 0.19 respectively).
Age:

Elderly: Population analysis of the pivotal clinical trial, showed that the steady state concentrations of rivastigmine was not influenced by age (p=0.72)
Pediatrics: Exelon patch was not investigated in children or adolescents.
Gender: Based on a population analysis, gender (107 males and 203 females) did not affect the steady state concentrations of rivastigmine (p=0.78)
Race: No meaningful race effect was observed.

EXTRINSIC FACTORS

No new drug interaction studies are conducted with Exelon Patch.

Is rivastigmine an inhibitor of CYP2B6 enzyme?

Rivastigmine or its metabolite is not an inhibitor of CYP2B6 enzyme.

Highlights of Pharmacokinetics of Exelon Patch formulation (including 15cm^2 patch size/27 mg total drug load).

- The pharmacokinetics of rivastigmine and NAP226-90 are similar in the AD patients and healthy volunteers when given the same patch size applied to the same body site (upper back).
- Rivastigmine exhibits nonlinear pharmacokinetics following both oral and intravenous administrations because of capacity-limited elimination. The patch formulation (5cm^2 - 20cm^2) also displays nonlinear rivastigmine pharmacokinetics which, however, was less pronounced than with the oral formulation.
- Dose over proportionality, fluctuation index, inter patient variability and metabolism were less for patch when compared to oral formulations.

Single Dose Pharmacokinetics:

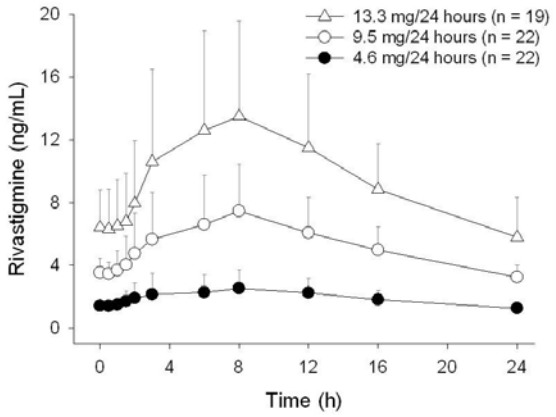
The single dose pharmacokinetic parameters of rivastigmine and its metabolite after a single 24 hour application of the 15 cm^2 patches Final Marketing Image (FMI) is given in the following table:

Table: Summary of single dose pharmacokinetic parameters (± SD (CV)) of rivastigmine (15 cm^2 patch) after a single 24 hour application of patch in healthy subjects (study 2335, n = 19)

Pharmacokinetic Parameter (units)	Mean ±SD (%CV)
C_{max} (ng/mL)	12.9 ± 4.27 (33.1)
t_{max} (h)	10.03 (8.0-16.0)
AUC_{0-24h} (ng.h/mL)	204 ± 71.9 (35.2)
AUC_{last} (ng h/mL)	237 ± 81.2 (33.1)

AUC_{inf} (ng.h/mL)	239 ± 81.2 (33.9)
$t_{1/2}$(h)	2.9 ± 0.37 (12.8)
Vz/F (L)	296 ± 98.4(33.2)
CL/F (L/h)	69.9 ± 17.1 (24.5)

Figure: Pharmacokinetic profile (± SD (CV)) of rivastigmine (15 cm^2 patch) after a single 24 hour application of patch in healthy subjects represented by open triangles (Δ, study 2335, n = 19)



With increasing doses of transdermal rivastigmine, the increase in exposure was slightly over proportional.

Multiple Dose Pharmacokinetics:

Two Clinical Pharmacology studies were conducted using repeated dose administrations. One study [Study 2331] was conducted in AD patients with 14 day application of rivastigmine patches 5 to 20 cm^2.

The other study [Study 1101] was conducted in Japanese healthy male volunteers given repeated daily applications for 5 days of rivastigmine patch of 5, 7.5 and 10 cm^2.

Both studies used a continuous application of the patches with no washout between treatments. Study 1101 also had the pharmacokinetic profile taken at the beginning of each period.

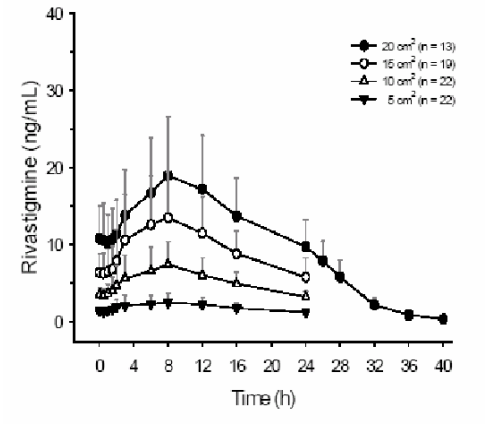
Rivastigmine and NAP226-90 exposure at steady state after a 14 day application of the Final Marketing Image (FMI) patch is given in the following Tables. In this study, PK profile at the beginning of each treatment was not taken.

The PK parameters after multiple dosing are shown in the following Table:

Table: Rivastigmine exposure parameters following rivastigmine multiple o.d. patch applications in AD patients (study 2331)

Rivastigmine	C_{max} (ng/mL)	t_{max} (h)	C_{avg} (ng/mL)	AUC_{24h} (ng·h/mL)	$t_{½}$ (h)	FI *
15 cm^2 (27 mg loaded dose, n = 19)						
Mean ± SD	14.1 ± 6.30	-	9.71 ± 3.47	233 ± 83.2	-	0.72 ± 0.36
CV%	44.6	-	35.7	35.7	-	50.5
Median	15.3	8.0	10.6	255	-	0.61
Range	4.32-25.7	3.0-16.0	3.89-14.4	93.3-345	-	0.08-1.30
Geo. mean	12.6	-	9.03	217	-	0.60
CV% Geo. mean	55.4	-	42.9	42.9	-	81.3

Figure: Rivastigmine plasma concentrations (mean +/- SD) following multiple dermal (o.d.) patch applications for 14 days



Compartmental analysis of PK parameter obtained from administration of different patch sizes of 5, 10, and 15 cm^2 showed an increase in rivastigmine exposure relative to the lowest dose (5 cm^2) by 2.6, 4.9 and 7.8 fold for the 10, 15 and 20 cm^2 patch, respectively.

Relative bioavailability to oral Capsule:

Following table shows relative bioavailability with the capsule formulation in a parallel design study of the Exelon patch (15 cm^2) compared to the oral capsule (1.5, 3, 4.5 and 6 mg BID) after 14 days of multiple dosing at each treatment level.

Table: Rivastigmine mean C_{max} and AUC_{24h} ratios of patch over capsule (reference) treatments

		Capsule			
		1.5 mg bid (3 mg/day)	3.0 mg bid (6 mg/day)	4.5 mg bid (9 mg/day)	6.0 mg bid (12 mg/day)
	C_{max}[1] (ng/mL):	3.34 ng/mL	9.70 ng/mL	16.8 ng/mL	29.3 ng/mL
	AUC_{24h} (ng·h/mL):	12.5 ng·h/mL	57.7 ng·h/mL	106 ng·h/mL	191 ng·h/mL
Patch					
15 cm^2	C_{max} = 14.1 ng/mL	4.22 **	1.45 *	0.84	0.48 **
	AUC_{24h} = 233 ng·h/mL	18.6 **	4.04 **	2.20 **	1.22

Exposure (i.e. AUC_{24h}) achieved following application of the 15 cm^2 patch was, on average, 1.2-fold higher than following the 6 mg b.i.d. (12 mg/day) oral dose, while the Cmax was 0.48- fold lower.

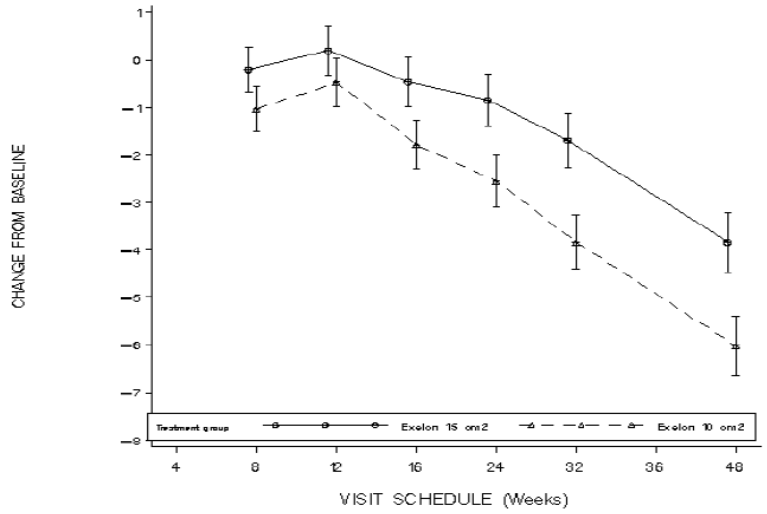
What are the characteristics of dose/effectiveness relationship for Exelon® 10 cm^2 and 15 cm^2 patch in patients with Alzheimer's disease?

The dose effectiveness relationship was compared for Exelon® 10 cm^2 and 15 cm^2 patch in patients with Alzheimer's disease in a single phase III pivotal efficacy study CENA713D2340 (Study D2340).

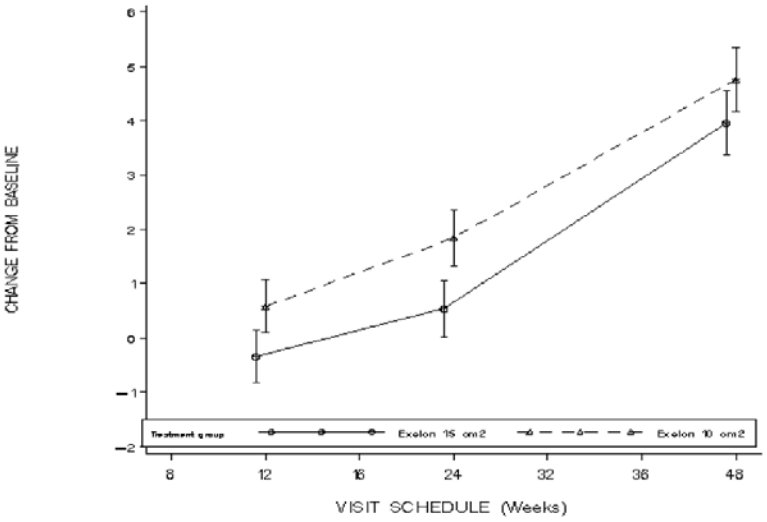
Study D2340 conducted in patients with mild to moderate Alzheimer's disease, was a 48-week, multicenter, randomized, double-blind, parallel group trial. The study evaluated the comparative efficacy, safety and tolerability of Exelon® 10 cm^2 and 15 cm^2 patch in patients with AD showing cognitive and functional decline while being treated with Exelon 10 cm^2 patch during an initial 24 to 48 week open-label treatment phase.

The data are presented for a total of 536 patients (Exelon 15 cm^2 N=265; Exelon 10 cm^2 N=271) in the intent to treat (ITT) population, with last observation carried forward (LOCF), unless otherwise specified. The co-primary efficacy analysis variables were the change from DB randomization baseline to DB Week 48 in the ADAS-cog total score and ADCS-Instrumental ADL score. Both co-primary outcome variables were analyzed using Analysis of Covariance (ANCOVA) model adjusted for country and baseline score.

ADCS-Instrumental ADL score change from baseline (LSM (SEM)) in the double-blind phase - Study D2340 (ITT-DB population, LOCF)



ADAS-cog total score change from baseline (LSM (SEM)) in the double-blind phase by treatment group - Study D2340 (ITT-DB population, LOCF)



The trial demonstrated a statistically significant effect on ADCS-Instrumental ADL (the co-primary global endpoint, p=0.002); however, the treatment difference on ADAS-cog (the co-primary cognitive endpoint, figure below) was not statistically significant (p=0.227). Since the trial needs to show statistically significant difference in both the co-primary end points, there is not sufficient evidence to support efficacy of Exelon 15 cm2 patch compared to Exelon 10 cm2 patch.

Jagan Mohan Parepally, Ph.D. Date
Reviewer
Division of Clinical Pharmacology 1

Angela Men, M.D., Ph.D. Date
Team Leader
Division of Clinical Pharmacology 1

cc: HFD-120 sNDA# 1822-083
HFD-860 Mehul Mehta, Ramana Uppoor, Angela Men, Jagan Mohan Parepally.

V. Appendix 1: Individual Study Report

Study Title	***In vitro assessment of CYP2B6 inhibition by ENA713 (PKF212-713) and its metabolite NAP226-90***
Study number	1100543
Objective	To determine the potential of ENA713 (PKF212-713) and its metabolite NAP226-90 to function as in vitro inhibitors of cytochrome P450 enzyme CYP2B6.

METHODS

Selective inhibition of bupropion hydroxylation:

Pooled human liver microsomes, test substrate (rivastigmine or NAP226-90) and probe substrate (bupropion) were incubated with an NADPH generating system, with or without CYP selective inhibitor (2µM AXR642 + 20µM tranylcypromine) in potassium phosphate (pH 7.4) at 37°C for 45 min. After 10 min of pre-incubation, the reactions were initiated by adding NADPH solution. Comparisons were made to bupropion metabolism (depletion of parent) in the absence of inhibitors to determine percent inhibition. The probe substrate concentration (25 µM) used was lower than Km values.

Microsomal incubation composition

Chemical	Final concentration
0.5 M potassium phosphate buffer, pH 7.4	50 mM
magnesium chloride	5 mM
pooled human liver microsomes in 50 mM potassium phosphate buffer, pH 7.4	0.1 mg protein/mL (see Table 3-4)
PKF212-713 or NAP226-90	0, 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, 100, 200 µM
positive control	mixture of 2 µM AXR642 and 20 µM tranylcypromine
probe substrate	25 µM bupropion (see Table 3-4)
NADPH	1 mM

Reviewer's Comment: Bupropion is an acceptable substrate for measurement of CYP2B6 activity. However, AXR642 or tranylcypromine are not listed in the acceptable inhibitors according to the Agency's guidance. Based on the published article, the CYP2A6 inhibitor tranylcypromine inhibited bupropion hydroxylation with IC_{50} values of 3.1. (ref: http://dmd.aspetjournals.org/content/32/6/626.full)

Analytical methods
All analyses were performed with validated LC/MS/MS method using isotopic internal standard.

Calculations of IC50 inhibition values

All absolute activities were converted into relative activities by the enzymatic activity without addition of inhibitor as 100% and recalculating the other activities relative to this number (S2). Enzyme inhibition parameters (IC50 values) were calculated using the kinetic equation:

$$y = \frac{100\%}{1 + \left(\frac{x}{IC50}\right)^{s}}$$

(x = concentration; y = relative enzyme activity; s = slope factor).

RESULTS

Following tables represent concentration of hydroxybupropion formation in the presence of different concentrations of the test substrate (rivastigmine or NAPP226-90) and positive control.

Effect of rivastigmine (PKF212-713) on CYP2B6-mediated hydroxybupropion formation in pooled human liver microsomes

PKF212-713 (µM)	hydroxybupropion formation (pmol/(mg protein • min))			relative activity (%)
	single value1	single value 2	mean	mean
0	248.1	187.2	217.7	100.0
0.78	237.1	194.4	215.7	99.1
1.56	198.0	188.8	193.4	88.9
3.13	212.5	177.5	195.0	89.6
6.25	215.6	191.1	203.3	93.4
12.5	217.4	188.1	202.8	93.2
25	233.6	182.9	208.2	95.7
50	223.4	201.6	212.5	97.6
100	201.2	188.9	195.1	89.6
200	133.3	151.3	142.3	65.4
pos ctrl	33.6	29.8	31.7	14.6

Effect of NAP226-90 on CYP2B6-mediated hydroxybupropion formation in pooled human liver microsomes

NAP226-90 (μM)	hydroxybupropion formation (pmol/(mg protein • min))			relative activity (%)
	single value1	single value 2	mean	mean
0	402.7	371.2	386.9	100.0
0.78	420.1	324.1	372.1	96.2
1.56	421.0	347.8	384.4	99.4
3.13	433.9	358.1	396.0	102.4
6.25	360.5	360.1	360.3	93.1
12.5	445.6	397.8	421.7	109.0
25	405.9	334.4	370.1	95.7
50	437.1	360.8	399.0	103.1
100	534.8	316.4	425.6	110.0
200	577.1	468.1	522.6	135.1
pos ctrl	80.5	66.4	73.5	19.0

At rivastigmine and NAP226-90 concentrations of up to 200 μM, no inhibition or relatively less inhibition of CYP2B6 at higher concentrations was observed.

Reviewer's Comment: The maximum concentration achieved by 15 cm^2 patch treatment in clinical studies is approximately 0.05 μM rivastigmine. The metabolites concentration is approximately 50-60% (0.02-0.03 μM) of the parent.

Determination of IC_{50} values

Test substance	CYP enzyme	Probe reaction	IC50 value (μM)
PKF212-713	CYP2B6	bupropion hydroxylation	> 200
NAP226-90	CYP2B6	bupropion hydroxylation	> 200

CONCLUSION

Based on this study, rivastigmine and its metabolite do not have a potential to inhibit CYP2B6 *in vivo*.

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/s/

JAGAN MOHAN R PAREPALLY
08/08/2012

YUXIN MEN
08/08/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: August 14, 2012

To: Teresa Wheelous
Senior Regulatory Management Officer
Division of Neurology Products (DNP)

From: Meeta Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion, Division of Consumer Drug Promotion (formerly known as Division of Drug Marketing, Advertising, and Communications [DDMAC])

CC: Twyla Thompson, Acting Group Leader, DCDP

Subject: NDA 022083
DCDP Comments for Exelon Patch (rivastigmine transdermal system)
Patient Package Information

DCDP has reviewed the proposed Patient Package Information (PPI) for Exelon patch. We do not have any additional comments at this time.

Thank you for the opportunity to comment on the proposed PPI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
08/17/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 8/16/2012

To: Teresa Wheelous, Sr. Reg. Management Officer
Division of Neurology Products (DNP)

From: Quynh-Van Tran, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)
Division of Professional Drug Promotion (DPDP)

Subject: NDA 022083/S-016
OPDP labeling Comments for Exelon Patch
(rivastigmine transdermal system) – efficacy supplement for the new dosage strength of 13.3mg/24h

---

This consult is in response to DNP's August 10, 2012 request for OPDP's review of proposed PI for an efficacy supplement on a new dosage strength of Exelon Patch 13.3mg/24 h (DNP version dated 8/6/12)

OPDP appreciates the opportunity to provide comments on the proposed PI. Please see attached PI with our comments incorporated therein.

If you have any questions, please contact me at 301-796-0185.

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/s/

QUYNH-VAN TRAN
08/16/2012

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	**Exelon Patch (rivastigmine transdermal system)**
Applicant	Novartis Pharmaceuticals
Application/Supplement Number	NDA 22,083/S-16
Type of Application	Efficacy supplement
Indication(s)	Mild to moderate dementia of the Alzheimer's disease type and mild to moderate dementia associated with Parkinson's disease
Established Pharmacologic Class[1]	acetylcholinesterase inhibitor
Office/Division	ODE1/DNP
Division Project Manager	Teresa Wheelous
Date FDA Received Application	October 31, 2011
Goal Date	August 31, 2012
Date PI Received by SEALD	August 6, 2012
SEALD Review Date	August 8, 2012
SEALD Labeling Reviewer	Eric Brodsky
SEALD Division Director	Laurie Burke

PI = prescribing information

[1] The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements for Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item **(deficiency)**.
- **YES:** The PI **meets** the requirement for this item **(not a deficiency)**.
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*

• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

NO 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment: *Change the proprietary name from title case to upper case in the Highlights Limitation Statement.*

Product Title

YES 10. Product title in HL must be **bolded.**

Comment: *Change the proprietary name from title case to upper case in the Product Title.*

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

NO 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment: *If approved the efficacy supplement provides for a great maximum maintenance dose (from 9.5 mg per 24 hours to 13.3 mg per 24 hours). This is a recent major change.*

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

NO 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment: *If approved the efficacy supplement provides for a great maximum maintenance dose (from 9.5 mg per 24 hours to 13.3 mg per 24 hours). This is a recent major change.*

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Selected Requirements of Prescribing Information (SRPI) Revised

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.
Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.
Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

NO 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.
Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.
Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

NO 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment: *The Drug Interactions title is not capitalized in the TOC.*

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

NO 32. All section headings must be **bolded** and in UPPER CASE.

Comment: *The Drug Interactions title is not capitalized in the TOC.*

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE

Selected Requirements of Prescribing Information (SRPI) Revised

11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "*[see Warnings and Precautions (5.2)]*".

Comment: *In Sections 2.1, 2.4, and 5.1, if there is no additional information in another section do not need to cross-reference to the Patient Information Counseling section (recommend removal of the cross-reference to "Patient Counseling Information" section). In Section 6.1, a cross-reference to Clinical Studies (14.2) is more specific than Clinical Studies (14).*

YES 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

N/A 45. If no Contraindications are known, this section must state "None".

Comment:

Selected Requirements of Prescribing Information (SRPI) Revised

Adverse Reactions

NO 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."

Comment:

YES 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

(b) (4)

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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/s/

ERIC R BRODSKY
08/08/2012

LAURIE B BURKE
08/09/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	July 24, 2012
To:	Russell Katz, M.D., Director **Division of Neurology Products (DNP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Associate Director for Patient Labeling Team **Division of Medical Policy Programs (DMPP)** Robin Duer, RN, BSN, MBA Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with Submitted Patient Package Insert (PPI)
Drug Name:	Exelon Patch (rivastigmine transdermal system)
Dosage Form and Route:	Topical Patch
Application Type/Number:	NDA 22083
Supplement Number	016
Applicant:	Novartis Pharmaceuticals

1 INTRODUCTION

On November 18, 2011, Novartis Pharmaceuticals submitted for the Agency's review a Supplemental New Drug Application (sNDA) for Exelon Patch (rivastigmine transdermal system). This supplement provides for a new dosage strength of the transdermal formulation, 15cm² (13.3mg/24 hours). Exelon Patch (rivastigmine transdermal system) is currently approved for the treatment of mild to moderate dementia of the Alzheimer's type (AD) and mild to moderate dementia associated with Parkinson's Disease (PDD).

On November 22, 2011 the Division of Neurology Products (DNP) requested that the Division of Medical Policy Programs **(**DMPP) review the Applicant's proposed Patient Package Insert (PPI) for Exelon Patch (rivastigmine transdermal system), 15cm² (13.3 mg/24 hours).

This memorandum documents the DMPP review and concurrence with the Applicant's proposed PPI for Exelon Patch (rivastigmine transdermal system).

2 MATERIAL REVIEWED

- Draft Exelon Patch (rivastigmine transdermal system), 15cm² (13.3 mg/24 hours) PPI received on November 18, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on July 17, 2012
- Draft Exelon Patch (rivastigmine transdermal system), 15cm² (13.3 mg/24 hours) Prescribing Information (PI) received on November 18, 2011, revised by the Review Division throughout the review cycle, and received by DMPP July 17, 2012
- Approved Excelon Patch (rivastigmine transdermal system) PPI dated August 27, 2010

3 CONCLUSIONS

In our review, we performed a side-by-side review of the Applicant's proposed PPI against the currently approved Exelon Patch (rivastigmine transdermal system) PPI dated August 27, 2010 and find the Applicant's proposed PPI is acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the Prescribing Information (PI) to determine if corresponding revisions need to be made to the PPI.
- Consult DMPP for a comprehensive review of the PPI at the next labeling opportunity. We recommend that the instructions for use imbedded within the PPI

be a separate document and attached to the PPI to be consistent with current patient labeling practices and for easier readability for the patient.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
07/24/2012

LASHAWN M GRIFFITHS
07/24/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label, Labeling and Packaging Review

Date:	June 26, 2012
Reviewer:	Jung Lee, RPh Division of Medication Error Prevention and Analysis
Acting Team Leader:	Chi-Ming (Alice) Tu, PharmD Division of Medication Error Prevention and Analysis
Associate Director:	Scott Dallas, RPh Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Exelon Patch (Rivastigmine Transdermal System), 13.3 mg/24 hours
Application Type/Number:	NDA 022083/S-016
Applicant:	Novartis
OSE RCM #:	2011-4274

*** This document contains proprietary and confidential information that should not be released to the public.***

Contents

1 INTRODUCTION

This review evaluates the proposed foil pouch label, carton labeling, and insert labeling for the new dosage strength of Exelon Transdermal Patch, 13.3 mg/24 hours (NDA 022083/S-016) for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

This prior approval supplement (NDA 022083/S-016) provides for the addition of a higher strength Exelon Transdermal Patch, 13.3 mg/24 hours, to the currently marketed Exelon Transdermal Patches. The product characteristics are the same as the currently marketed Exelon Transdermal Patches.

1.2 REGULATORY HISTORY

Exelon Transdermal Patch, 4.6 mg/24 hours and 9.5 mg/24 hours, was approved on July 6, 2007.

1.3 PRODUCT INFORMATION

The following product information is provided in the February 14, 2012 submission.

- Active Ingredient: Rivastigmine
- Indication of Use: Treatment of mild to moderate dementia of the Alzheimer's type and mild to moderate dementia associated with Parkinson's disease.
- Route of Administration: Transdermal
- Dosage Form: Transdermal Patch
- Strength:13.3 mg/24 hours
- Dose and Frequency: Initiate treatment with the 4.6 mg/24 hours Exelon Patch. Dose increases should occur only after a minimum of 4 weeks at the previous dose, and only if the previous dose has been well tolerated. The recommended maintenance dose of 9.5 mg/24 hours and should be maintained for as long as therapeutic benefit persists. Based on the prescriber's assessment, patients can then be increased to the 13.3 mg/24 hours dose and maintained.
- How Supplied: Exelon Patch 13.3 mg/24 hours (15 cm^2 contains 27 mg of rivastigmine base with in-vivo release rate of 13.3 mg/24 hours), Carton of 30 patches
- Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Keep Exelon Patch in the individual sealed pouch until use. Each pouch contains one patch. Used systems should be folded, with the adhesive surfaces pressed together, and discarded safely.
- Container and Closure System: (b) (4) [redacted]

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Exelon Transdermal Patch medication error reports. We also reviewed the Exelon Transdermal Patch labels and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	March 28, 2012
Drug Names	Active Ingredient: Rivastigmine Active Ingredient: Rivastigmine tartrate Trade Name: Exelon Verbatim Term: Exelon% Verbatim Term: Rivastig%
MedDRA Search Strategy	Medication Errors (HLGT) Product Quality Issue (HLGT)
Time Limitation	From April 28, 2010 (Date of last search in OSE Review # 2010-869) to March 28, 2012

The AERS database search identified 106 reports. Each report was reviewed for relevancy and duplication. After individual review, 80 reports were not included in the final analysis for the following reasons:

- Adverse drug reactions not related to a medication error
- Medication errors unrelated to Exelon Patches' label and labeling
- Exelon Patch application site reactions
- Duplicate reports
- Foreign cases because the foreign carton labeling and insert labeling may differ from the labeling in the United States

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Foil Pouch Label submitted April 4, 2012 (Appendix B)
- Carton Labeling submitted October, 31, 2011 (Appendix C)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Insert Labeling submitted February 14, 2012

2.3 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed Exelon on May 24, 2010 (OSE Review # 2010-869) and we looked at this review to ensure all our recommendations were implemented. All recommendations were made to the insert labeling and patient labeling for Exelon Patch. Recommendations to improve the Dosage and Administration, Warnings and Precautions, Overdose, and Patient Information sections of the insert labeling were made in the August 2010 revisions. The most notable revisions included changes or additions of the statements to mitigate the risk of medication errors occurring due to the use of multiple patches at one time, failure to remove old patches before applying a new patch, patches being cut in half, instructions for how to properly dispose of the patch, what to do if the patch falls off, and instructions to wash your hands after applying the patch to avoid accidental exposure.

3 MEDICATION ERROR RISK ASSESSMENT

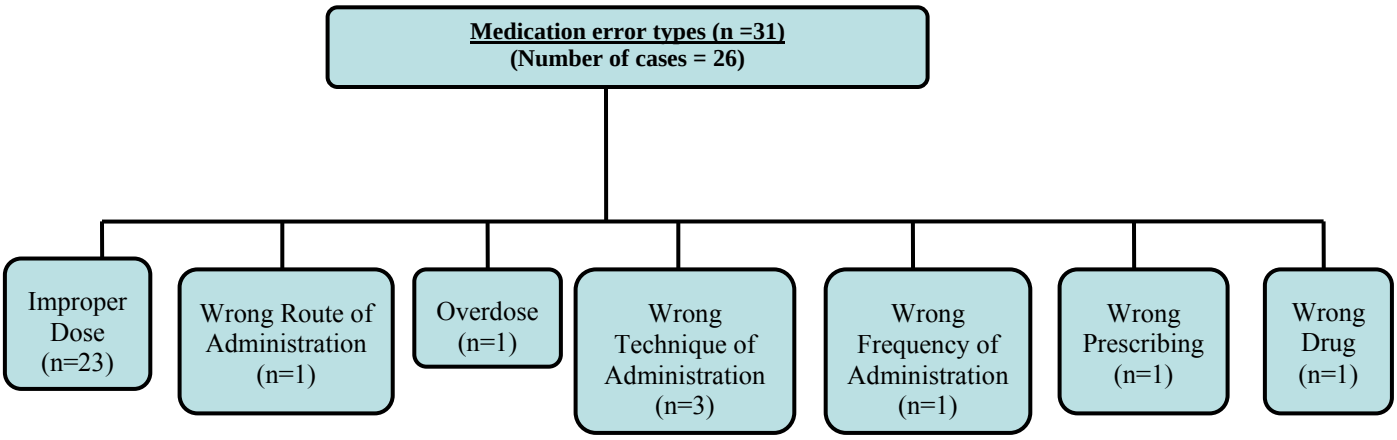
The following sections describe the results of our AERS search and the risk assessment of the Exelon Transdermal Patch product design as well as the associated label and labeling.

3.1 MEDICATION ERROR CASES

Following exclusions as described in section 2.1, twenty-six Exelon Transdermal Patch medication error cases remained for our detailed analysis. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the type and factors contributing to the errors when sufficient information was provided by the reporter[2]. Figure 1 provides a stratification of the number of cases included in the review by type of error. We note that the sum of the number of medication error types (n=31) is higher than the number of AERS cases (n=26) because four cases reported two or more error types. Appendix D provides listings of all relevant ISR numbers and the full narratives for the cases summarized in this review.

[2] The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website http://www nccmerp.org/pdf/taxo2001-07-31.pdf. Accessed June 1, 2011.

Figure 1: Exelon Transdermal Patch medication errors categorized by type of error (n = 31)



3.1.1 Wrong Drug (n=1)

One case of wrong drug (ISR #7937786-5) reported a patient taking one Exelon capsule instead of applying one 9.5 mg/24 hours patch because he ran out of his patch and could not obtain any patch at his local pharmacy. As a result of switching to the capsules, he experienced delusions, hallucinations, bad dreams and dizziness.

3.1.2 Wrong Prescribing (n=1)

One case (ISR # 7775386-0) described a doctor instructing the patient to use two of the 4.6 mg/24 hours patches since the patient had some left over from their previous prescription. The patient experienced tiredness, depression, weight loss, sensitivity and itching.

Our review of the insert labeling found that it is unclear as to whether the practice of using two lower strength patches to equal the dose of a higher strength patch is clinically acceptable. However, there are clear warnings against applying more than one patch at a time throughout the insert labeling, on the foil pouch label, and on the carton labeling; therefore, no further recommendations are needed at this time.

3.1.3 Wrong Frequency of Administration (n=1)

A case of wrong frequency was reported where the patient's husband was applying one patch every 6 days rather than the once daily dose due to the husband's concerns about the patient's reaction of stupor from the drug.

The most current foil pouch label and carton and insert labeling (revised August 2010) clearly state that the patch is to be applied once daily or changed every 24 hours. This case was initially received in December 2010, after the label and labeling revisions went into effect. Since the frequency of administration is adequately addressed in the revised labeling, no further recommendations are needed.

3.1.4 Wrong Route of Administration (n=1)

We identified one case of wrong route of administration error where an Exelon Patch was ingested by the patient. The patient experienced agitation, restlessness but otherwise presented with stable vital signs. No root cause was provided for why the patient may have ingested the patch.

Based on this case, we reviewed the labels and labeling to determine if it was clear that Exelon Patch was to be used externally and not to be administered orally. The route of administration statement is included on the back panel of the carton labeling, foil pouch label and throughout the Dosage and Administration and Patient Information sections of the insert labeling. In addition, the established name contains the dosage form "transdermal system" further indicating that the product is to be used externally. Since the route of administration statement is currently on the back panel of the carton labeling and foil pouch label, we recommend moving the statement "For Transdermal Use Only" to the principal display panel to further reinforce the proper route of administration for Exelon Patch.

3.1.5 Overdose (n=1)

One case of overdose described a patient who developed visual hallucination, myalgia and diarrhea as a result of having his/her dose increased from 4.6 mg/24 hours to 9.5 mg/24 hours by the doctor. The patient's dose was later reduced to the 4.6 mg/24 hours patch. It is unclear from the narrative if the dose was titrated to the maintenance dose of 9.5 mg after the recommended minimum time of 4 weeks. If the minimum time to increase the dose was not observed, this may explain the patient's reaction to the higher dose.

Upon review of the Dosage and Administration section of the insert labeling, we find that it clearly states that treatment is to be started with Exelon Patch 4.6 mg/24 hours and then after a minimum of 4 weeks of treatment, if well tolerated, the dose should be increased to 9.5 mg/24 hours which is the recommended effective dose.

3.1.6 Wrong Technique of Administration (n=3)

The first case (ISR # 6980541-3) described a patient who cut his Exelon patch in half in hopes of reducing his dose because he was experiencing bowel movement problems with the higher strength. The patient reported having no adverse outcomes from cutting the patch in half.

The second case (ISR# 7596011-8) reported that a nursing home nurse was going to apply an Exelon patch that had been folded in half to the patient's back using tape and on another occasion did apply half of a patch to the patient. As a result of these events, the patient experienced weight loss, blurred vision, depression and confusion.

In the third case (ISR #7130282-7), the patient's husband was applying the patch to the same spot for 14 days without changing the application site as instructed in the Patient Information section under "How should I use Exelon Patch" of the insert labeling. The root cause was attributed to the husband's inattention to the need to rotate the patch application site.

Our review of the label and labeling found clear and adequate warnings not to use the patch if they are cut, damaged or changed in any way. Under the Dosage and Administration section and in the Patient Information section under the heading "Apply Exelon Patch as follows", it clearly states that the patch should not be used if cut, damaged, folded sharply or changed in any way. The foil pouch also contains a warning not to cut the patch.

In regards to rotating the application site, the inside panel of the carton labeling does state to change the location of each new patch. Additionally, the Dosage and Administration and Patient Information sections of the insert labeling also state to not apply a new patch to the same spot for at least 14 days. However, the foil pouch label lacks this same information. We recommend including the statement "Change the location of each new patch" on the back panel of the foil pouch label to ensure consistency in labeling.

3.1.7 Improper Dose (n=23)

We received 23 cases of patients who received an improper dose of Exelon Patch. Sixteen out of the 23 cases was due to failure to remove the previous patch before applying a new patch or due to multiple patches being applied at one time, leading to an overdose and clinically resulted in elevated blood pressure, bradycardia, unresponsive, respiratory depression, confusion, disorientation, agitation, worsening dementia, weight loss, blurred vision, depression, abdominal pain, nausea, vomiting, dehydration, dizziness, headache, lethargy, low blood sugar, or hospitalization. One of the 23 cases reported a dose omission in which the patient went without the patch for ten days then went back on the patch but applied 2 to 3 patches at one time. The patient was not able to walk and experienced severe dehydration as a result of applying multiple patches at once.

Three of the 23 improper dose cases mentioned a root cause. Two of the three cases (ISR # 7775386-0, 7047341-X) attributed the error to forgetfulness and not to the misunderstanding of labeling instructions. The outcomes from these 2 cases included red spots on the patient's back from the adhesive and being tired, depressed, weight loss, sensitivity and itching. The last of the three cases (ISR # 8154825-X) involved the patient's wife who could not find the previous patch on the patient's body and assumed that the hospital staff had taken it off and proceeded to apply a new patch only to find the old patch the following day still on her husband. No outcome was reported in this case.

Additionally, another three cases of improper dose (ISR # 7577807-5, 7775386-0 and 7937786-5 which were initially received on March 9 and September 14 and 23, 2011, respectively, after the label and labeling revisions went into effect) involved patients who applied two patches of Exelon 4.6 mg/24 hours patch to equal the 9.5 mg/24 hours dosage. Two of the three cases described the patient initiating the application of the two lower dose patches, therefore, these two cases were categorized as an improper dose. In the third case, the doctor had instructed the patient to use two of the 4.6 mg/24 hours patches (wrong prescribing) since the patient had some left over from their previous prescription and the patient forgot to remove one of the two patches before applying a new patch (improper dose). The patients in these three cases experienced either an application site reaction such as itching as well as symptoms of tiredness, weight loss, depression, hallucinations or delusions.

Based on these cases, we reviewed the current label and labeling for Exelon Patch to determine if the instructions were included and if they clearly addressed the removal of the previous patch before applying a new patch and if it included instructions to only apply one patch at a time. Our review of the label and labeling found this information is adequately stated. The statement "Only one patch should be worn at a time" and the directions to remove the previous patch before applying a new patch and to rotate the location of each new patch is provided in bold font on the inside panel of the carton labeling. In addition, these statements can be found under the Patient Information section and the Dosage and Administration sections of the insert labeling.

3.2 ASSESSMENT OF THE PROPOSED 13.3 MG/24 HOURS PATCH STRENGTH

We evaluated the safe use and the risk of medication errors associated with the proposed addition of the higher strength, 13.3 mg/24 hours Exelon Transdermal Patch, to their existing 4.6 mg/24 hours and 9.5 mg/24 hours strengths. The proposed 13.3 mg/24 hour strength will be packaged in a pink colored foil pouch and carton which are adequately differentiated from the 4.6 mg/24 hours and 9.5 mg/24 hours packaging (beige and light grey color, respectively). All three strengths will share the same beige patch color and the same dark beige color text on the patch but the patch size will be 5 cm^2, 10 cm^2 and 15 cm^2 for the 4.6 mg, 9.5 mg and 13.3 mg, respectively, giving them adequate size differentiation.

The majority of our AERS cases identified reports of improper dose resulting in overdose in which patients were applying more than one patch at a time as a result of not removing the previous day's patch or applying multiple patches at once. In addition, three wrong technique errors were identified in which a patient applied a patch that had been cut or where the nurse had applied a cut and a folded patch onto a patient and a case where the patch site was not changed for 14 days. No root cause was provided in many of these cases so we cannot assess whether the cause was due to the current label and labeling or due to other factors such as the status of the patient's disease. Exelon is indicated for mild to moderate dementia from Alzheimer's or Parkinson's disease; therefore, patients with varying states of dementia may or may not understand the instructions that are provided on the label and labeling so any new recommendations to the labeling may not mitigate these medication errors we are seeing with Exelon. We note that the current insert labeling and carton labeling address all these issues but the foil pouch label lacks

this same information. We recommend including the statement "Change the location of each new patch" on the back panel of the foil pouch label to ensure consistency in labeling.

4 CONCLUSIONS

DMEPA concludes that the proposed label and labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product and to mitigate any confusion.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA supplement:

5.1 COMMENTS TO THE APPLICANT

A. Carton Labeling

1. Medication errors associated with wrong route of administration have been reported in post-marketing use. Relocate the route of administration statement, "For Transdermal Use Only", which is currently on the back panel of the carton labeling and pouch label to the principal display panel directly below the statement of strength to reinforce the proper route of administration for this product. Additionally, we recommend this labeling revision be implemented on the 4.6 mg/24 hours and 9.5 mg/24 hours carton labeling at the time of the next printing.

B. Foil Pouch Label

1. Include the statement "Change the location of each new patch" on the back panel of the foil pouch label following the statement "Apply patch to intact skin immediately after removal from pouch". To allow space for this statement, relocate the route of administration statement to the principal display panel (See Comment A1 above). Additionally, we recommend this labeling revision be implemented on the 4.6 mg/24 hours and 9.5 mg/24 hours foil pouch labeling at the time of the next printing.

If you have further questions or need clarifications, please contact Laurie Kelley, project manager, at 301-796-5068.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

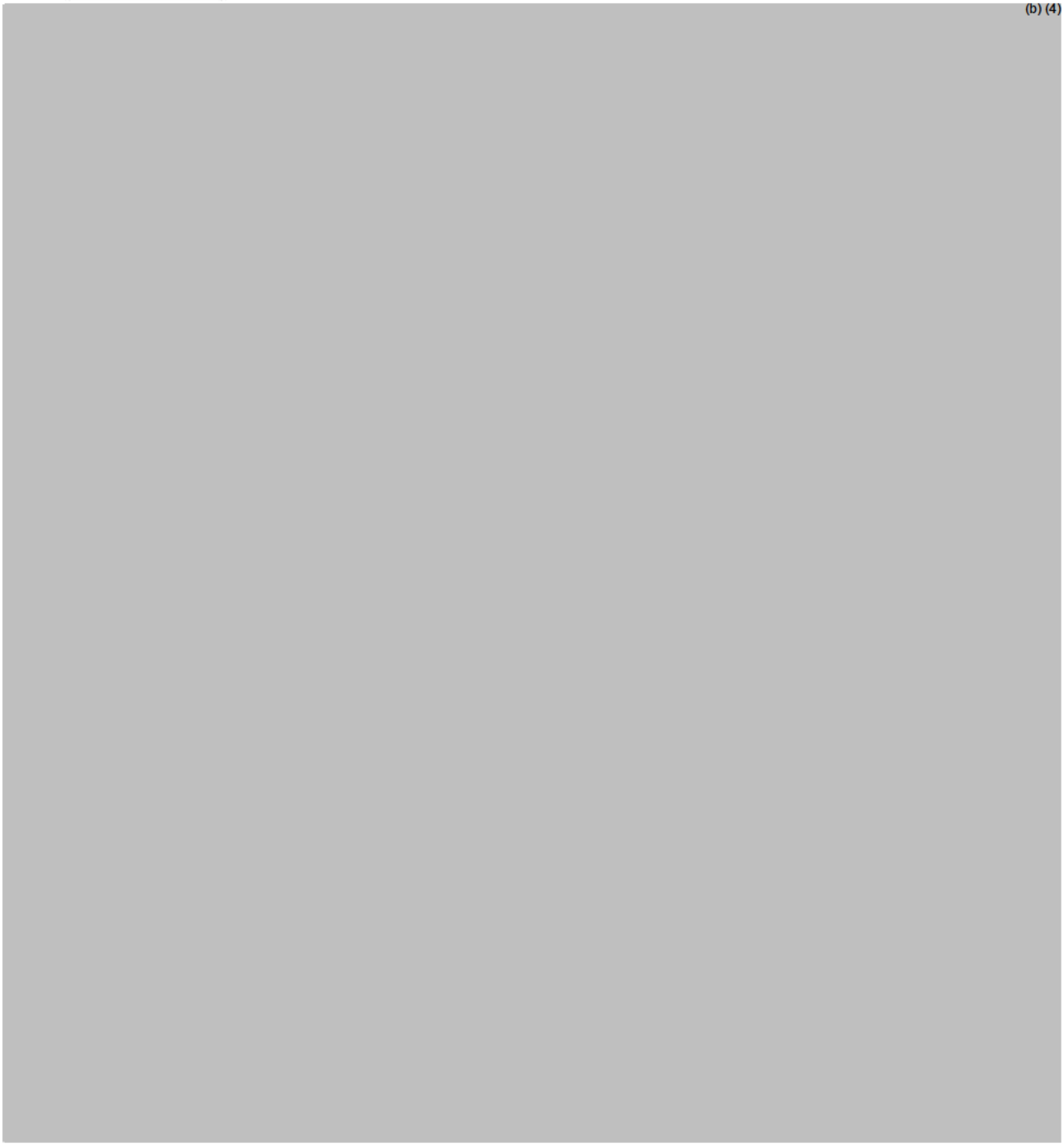
Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

Appendix B: Foil Pouch Label

Appendix C: Carton Labeling



Appendix D: ISR numbers of cases discussed in this review

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
6751068-9	Improper Dose	Overdose	Unresponsive, HBP, bradycardia	Initial nurse report was received on (b) (6) This elderly patient was treated with Exelon patch (rivastigmine) since (b) (6) for an unspecified indication. On the same day, the patient, who was in a nursing home, was found to be unresponsive with her blood pressure elevated (unspecified). The patient was taken to the hospital and at the hospital it was found that the patient had two Exelon patches. The patient was hospitalized. The action taken with the drug and the outcome of the event was not reported.Follow up received on 20 May 2010 from pharmacist: This polymedicated patient was treated with transdermal Exelon patch (rivastigmine) 9.5 mg per 24 hour, one patch daily, for dementia since 10 June 2009. On 01 May 2010, the patient applied first patch. The following day on (b) (6), the **second patch was applied without removing the first patch**. The patient became unresponsive and her pupils got fixed. The same day, her blood pressure rose to 204/80 and her heart rate was 57, her right side of the face drooped and was unable to arouse and the patient was hospitalised. As per cardiology in the hospital she was also found to have symptomatic bradycardia (heart rate lowest-39). The two Exelon patches were removed. During hospitalisation on (b) (6), her head CT scan was unremarkable while her MRI showed no evidence of new stroke. Her white blood cell count was 8.5, haemoglobin was 11.9, hematocrit was 37.1 while troponin and urine analysis was found to be negative. Her Chest X-ray was found to be normal. Since hospitalisation her blood pressure and heart rate kept on fluctuating. No recommendations from cardiology or neurology were made. There was a questionable TIA and her mental status also had improved. The patient had recovered from unresponsiveness, pin point pupils fixed, elevated blood pressure and symptomatic bradycardia. The reporter did not provide the outcome for right sided facial droop unable to arouse, questionable TIA while her mental status mental status had improved. The patient was discharged on (b) (6). The reporter assessed the event of unresponsiveness, pin point pupils fixed, elevated blood pressure as unrelated while the event of symptomatic bradycardia as related to the drug.
6856909-2	Improper Dose	Overdose	No ADR	Initial report received from a pharmacist on 06 Jul 2010: This patient was treated with Exelon (rivastigmine) transdermal patch 4.6 mg since an unknown date for dementia. This patient was in t nursing home and since an unknown date, the **nurse applied a new patch every day to the patie the old patch was not removed. On the fourth day the patient had 5 patches on totally, four previous days and a new on.** The reporter said that the patient was ok. No adverse events were reported. The action taken with the drug and outcome of the event was unknown.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
7022152-X	Improper Dose	Overdose	Confusion & Disorientation	Initial report received from physician on 21 Sep 2010: This patient was on treatment with Exelon (rivastigmine) trans therapeutic system patch for unknown indication with unknown dose since an unknown date. On an unknown date, the patient came to emergency room with complaints of confusion and disorientation. On examination it was found that, **patient had 4 Exelon patches on the body.** The patches were removed and symptoms improved. The final outcome of event was reported as resolved. No other information was available.
7047341-X	Improper Dose	Overdose	Red spots on back from adhesive	Initial consumer (patient's wife) report received on 28 May 2010: This diabetic patient was on Exelon patch 9.5 mg (rivastigmine; batch number 0489A, expiry date Nov 20) for an unspecified indication since an unknown date. **The reporter stated that when the patches were removed from the patient's back, there were red spots left on patient's skin but they did not itch. There was a problem with sticking of patch. There were also imprints left on the application site of patient.** Reporter also mentioned that, patient was being tired all the time. On an unspecified date, the patient was hospitalized where it was **forgot to take off the previous days patch**. Therefore the patient got an overdose on the medication. Final outcome of the event was not reported.Follow up report received from consumer (patient's wife) 04 Jun 2010: This patient was on Exelon patch treatment for a year. The patient experienced a big red marks on back after the patches were removed. The reported stated that the marks were all over the patients back and it left imprints on patient's clothes and on bed sheet. The reporter received a letter asking for the patient's doctor for information and she replied that she will work on it during weekend. No additional information was obtained.Follow up report received from consumer (patient's wife) on 17 Jun 2010: Reporter stated that, "she has taken the patient to neurologist and the red marks which patient had experienced were due to tape on Exelon patch and that he was allergic to tape and not Exelon.Follow up quality complaint report (no. 201003621) received on 06 Oct 2010: The investigation revealed that this was the first complaint received for each nature for the lot. The criticality of the defect was reported as no technical defect found. Lack of adhesion was the common issue with the TTS product. The adhesion was mainly determined by the properties of the human skin which show strong individual differences and might even vary seasonally. The final analysis showed that the Exelon Patches adhesive strength met the product specifications. Consecutively it was confirmed that the observed lack of adhesion was not due to a defect in production.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
7128012-8	Improper Dose		Hospitalized due to cardiovascular accident (Related to Exelon?)	Initial report received on (b) (6) from a nurse: This patient was on treatment with Exelon patch (rivastigmine) 9.5 mg for Alzheimer's disease was **administered a 2nd patch and the first one was not removed** on (b) (6). The patient was seen in a hospital and the patch was removed the next day. It was reported it was unclear if the patient was sent to the hospital due to the 2nd patch or because of a CVA (cardiovascular accident). The patient was currently still hospitalized. Action taken with Exelon and outcome was not provided.Follow up report received from a nurse on (b) (6): It was reported that, there was no adverse event and patient was doing fine. The patient did not fill out the adverse event form for any additional information and hence this case was closed.
7130282-7	Improper Dose, Wrong Frequency, Wrong Technique	Overdose	Wt loss, blurred vision, depression and other confusion	Initial report received from a consumer (patient's sister) on (b) (6): This patient who was also on antidepressants had medical history of Parkinson's disease. She started treatment with Exelon (rivastigmine) patch dose unknown for dementia for approximately a year or so (unspecified date). **The patient's husband felt that she goes stupor with the medication and he was putting 1 patch on every week or every 6 days.** The patient had gone into crazy state of mind. **Patient's husband hasn't paid attention not to put the patch on the same spot for 14 days.** The patient body weight was only 90 pounds and reporter thought that the 9.5mg is just too much for her sister. **Last year (date unknown) reporter noticed 2 instances where her sister's husband did not remove the old patch after applying the new one.** While talking the patient can't even finish a sentence and she's scared because she can't put things together. The patient was having blurred vision, depression and other confusion. The patient had lost weight, doesn't have the appetite to eat. She looked anorexic because she was with skin and bones. The patient had already experienced blurred vision with Sinemet solution (carbidopa, levodopa). It was reported that it was also difficult to determine if it's because of Exelon Patch or Sinemet. The outcome of the events was not reported.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
7229644-9	Improper Dose	Overdose	Agitated, worsening dementia	Initial report received from a consumer (patient's daughter) on (b) (6): This patient was treated with Exelon patch (rivastigmine) 4.6 mg for an unknown indication since 24 Sep 2010 (for 16 days). It was reported that due to some communications the **patient applied two patches for 10 more days** and this caused her to be extremely agitated and her dementia got exacerbated. It was further reported that the patient experienced high anxiety and delusional problems and also the patient became lethargic after the treatment with anti-anxiety drug. The reporter stated that the patient was brought to the hospital last night. The outcome of the event was not reported. No further information was provided.Follow up report received physician on 10 Jan 2011: This poly medicated patient was on treatment with Exelon 9.5 mg/24 hr, one patch daily for dementia type Alzheimer since 18 Oct 2010. The treatment with Exelon patch was discontinued on 21 Oct 2010 because **patient was applying two patches and patient was becoming agitated and crying**. It was reported that the patient was not been doing good for 4-5 days as she was crying for no reason, wakes up in the middle of night and started crying. The patient did not comprehend as well as she was doing before. The patient was having a lot of behavior problem and she was very emotional. The patient was requiring Alprazolam on a periodic basis and she did not want to use this medication as this medication made her very sleepy. It was reported that, **the patient was started Exelon patch 4.5 mg one patch daily but a couple of days patient's husband was applying two patches daily**. The patient was receiving the Lexapro 20 mg daily and Wellbutrin XL. The treatment with Exelon patch was discontinued. The outcome of agitation was recovered but for other events it was not reported. The seriousness criteria of agitation was non serious and causality as suspected.
7487722-3	Improper Dose	Overdose	Vomiting, dizziness, HA, lethargic	Case number PHHO2011US07896 is an initial report received on 05 May 2011, from clinical study CENA713DUS44E1. This 79-year-old female subject (centre number 648, subject number 8) was enrolled In CENA713DUS44E1 (A 24 Week Open-Label Extension to Study CENA713DUS44 (A 24 Week, Prospective, Randomized, Parallel-Group, Double-Blind, Multi-Center Study Comparing the Effects of Rivastigmine Patch 15 cm2 vs. Rivastigmine Patch 5 cm2 on ACTivities of Daily Living and CognitION in Patients with Severe Dementia of the Alzheimer's Type (ACTION)). The subject's medical history included mitral valve prolapse (1990), constipation (2010), rectocele and cystolcele (1962), hypothyroidism (1990), allergy to penicillin, urinary incontinence, acute angle closure glaucoma (1995), status post cataract surgery, stasis dermatitis (2010), hysterectomy due to dysfunctional uterine bleeding, status post Caesarean section (for fifth pregnancy), eczema and burns to arms / hands (1974). Concomitant medications included Tylenol (knee pain), Centrum, Lasix (leg oedema), Miralax (constipation), potassium chloride (leg oedema), Risperdal (agitation), Ativan (anxiety), Namenda (Alzheimer's disease), pravastatin (hypercholesterolemia), Joint-Ritis (knee and shoulder pain), vitamin B12, vitamin D3, timolol eye drops (glaucoma) and nystatin ointment (skin rashes). The subject

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
				completed the double blind phase of the study on 09 Mar 2011 without experiencing any significant adverse event. Informed consent for the extension study was signed on 09 Mar 2011. At this time, vital signs, physical examination, neurological examination, ECG (electrocardiogram) and laboratory tests were within normal limits. The daughter / caregiver assumed full responsibility for the storage and administration of the study medication. Prior to dispensing the study medication, oral and written instructions were given to the daughter / caregiver which were also attached to the study medication. The subject commenced extension phase study medication on 10 Mar 2011 at a dose of 10cm^2. The subject came for follow up titration visit on 14 Apr 2011 with no report or signs / symptoms of any adverse event. Exelon transdermal patch 15cm^2 was started on 15 Apr 2011. On 24 Apr 2011, the subject's live in home health aide went away on vacation and the daughter / caregiver took over the responsibility of applying the patch of study medication. At about 9am that day**, the caregiver applied 2 patches instead of a single patch as stated in the protocol**. Later that evening, the **subject complained to be feeling sick and subsequently had an episode of vomiting**. The subject did sleep through the night without any complaints. During the early hours on Monday 25 Apr 2011, the subject had another episode of vomiting. She also complained of dizziness and headache. The caregiver described the subject as lethargic with no desire to eat. There was no associated diarrhoea or other symptoms. Oral temperature was 97.6F. Two patches of study medication were again applied at about 9am. The subject later complained of headache and dizziness during the day and was given pepto-bismol to alleviate her gastrointestinal symptoms. The caregiver ascribed the subject's symptoms to food poisoning due to the Easter dinner which had resulted in two other family members experiencing the same symptoms. The subject was put to bed and slept through the night without incident. On Tuesday 26 Apr 2011, at 9am, **the caregiver again applied 2 patches of study medication.** The subject experienced no vomiting and continued to look lethargic and was without appetite. In the early afternoon**, the caregiver suspected that the signs and symptoms the subject was experiencing may have been due to the study medication and subsequently realised that she had been administering an extra patch of study medication. Both patches were then removed. The subject's symptoms promptly diminished and her condition returned to normal** by the morning of 27 Apr 2011. Since this date, the subject continued to receive one patch with no recurrences of symptoms or other side effects. On 29 Apr 2011, the subject's daughter / caregiver left a message with the investigator stating that the subject must have had an adverse event to the study medication. These events were assessed as serious and medically significant by the Investigator. The investigator reported that the event was suspected to treatment with the study medication.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
7573275-8	Improper Dose	Overdose	constant daze dizzy half the time sleepy, and sleeping a lot more	Case number PHHY2011US52225 is an initial spontaneous report received from a consumer on 13 Jun 2011. This report refers to a male patient. The patient's concomitant medication included Vitamins, Lipitor, Norvasc and Flomax. **The patient received Exelon Patch (rivastigmine) 4.6 mg twice daily** for memory since an unspecified date (since last month). The reporter stated that he felt like he was 'in a constant daze dizzy half the time sleepy, and sleeping a lot more, especially in the middle of the day it was making him woozy'. On an unspecified date the **patient cut his own dose to one patch per day. The reporter added that on an unspecified date the patient had put 4 or 5 patches on his back because he thought them as bandages and was hospitalized.** The outcome of the event was not reported.
7577807-5	Improper Dose	PQI	“Not doing very well”	Initial report received from a consumer on 23 Feb 2011: This is also a quality complaint (AQWA 179862) report. This poly medicated patient with underlying diabetes started treatment with Exelon patch 4.6 mg/24hours (rivastigmine; lot number 0760BA) for an unknown indication from an unspecified date. The patient complained that she was not doing very well. Also, she was disabled and could not move very fast. No event onset dates were provided.Follow up report received from the physician on 15 Jun 2011: This is also product quality complaint report (179862). The patient had medical history of nausea and heart burn. The patient started treatment with Exelon patch at 4.6 mg daily for an unspecified indication. The patient stated that, she was using alcohol to clean the area before applying Exelon Patch. It was reported that, medicated patient was disabled. She mentioned that, she had a cold and **adhesion issue with Exelon patch**. She **was using 4.6 mg Exelon patch that she had left over before her dosage was increased and double up with those to make up the 9.5 mg dosage.** It was reported that, some of the patches in current box sticks too hard and could not get them off. Some of them do not stick on all the day and she does not had enough sometimes to last the month. She feels that she had not getting the proper dosages. She had knee replacement on (b) (6), after that she was placed in a skilled nursing facility. The final outcome of the event was not reported.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
7596011-8	Improper Dose	Overdose, Wrong Technique	Vomiting, dehydrated, sick in stomach	Case number PHHY2011US26756, is combined initial and follow up spontaneous report received from consumer (patient's daughter) on 30 Mar 2011 and 01 Apr 2011 with follow up report received from a consumer (patient's daughter) on 05 Apr 2011 and follow up received from consumer (patient's daughter) on 19 Apr 2011 with combined follow up report received from consumer (patient's daughter) on 19 Apr 2011 and 20 Apr 2011 with follow-up report received from a consumer on 28 Apr 2011 with combined follow-up report received from consumer on 04 May 2011 and 09 May 2011, with the follow up received from the physician's staff on 29 Jun 2011. This report refers to 84 year old female patient. The polymedicated patient was treated with Exelon (rivastigmine) patch 4.6 mg once daily for an unknown indication since an unspecified date. The reporter **stated that in the nursing home her mother had double patching without following the directions for applying the patch and co-operating. On 30 Nov 2009, she had more than two patches on at the same time. The reporter believed that, the old patch was never removed before the new one was placed. The patient had been double patched at least twenty times since 23 Nov 2009, which had been applied by nurses in a nursing home. The reporter provided the dates as 03 May and 10 May 2010, 27 Nov 2010, 05 and 15 Dec 2010 and 18 Mar 2011 on which the patient had more than one patch. The patient had been triple patched on 19 Mar 2011.** On 26 Mar 2011 the patch was applied to the middle of the breast and on the bra line area of the middle of the back on 31 Mar 2011. The reporter found the patch on her mother breast soft tissues where her skin sags towards her nipple. The reporter stated that her mother had urinary tract infection all the time; it was scored 8 on 1-10 scale, muscle weakness and tiredness. The patient also had an upper respiratory infection and was diagnosed with diverticulosis. The reporter also mentioned that the patient experienced brain hemorrhage on 04 Jun 2010 and not on 06 Jun 2010 as earlier reported while being on the patch. Since the patient had brain hemorrhage she was not able to feed herself and she was on mechanically soft diet. The patient had been hospitalized 7 times for dehydration because they did not give her water. **The reporter stated that they keep putting the patch in the wrong place, it had been on her stomach, it had been near her elbow, and they have put it on her breast. It seemed to her since the patch was vertical it did go up and down the chest area and this could be misconstrued.** On an unspecified date, the patient was confused about what was going on. It was reported that, **the patch was folded in half once and the nurse was going to tape the patch on back and there also was one time when they put the patch on it was in half.** On night before this report the patient was exhausted but it was probably because of getting to bed too late last night. On 12 Apr 2011 it was on the back of left arm. On 16 Apr 2011 and 17 Apr 2011 the patch was exactly in the same spot. The patient then had hemorrhoids. The patient also had scaling on the sides of her nose. The reporter also stated the patient was taken off of physical therapy and was hospitalized twice. The patient was again diagnosed with hemorrhoids on 18 Apr 2011. It was reported that the

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
				patch was placed on patient's chest for 2 days and would put her in danger and the nursing home was out to kill the patient. The patient's hairs were greasy and would not remove as it hurt like bandaid. The reporter noticed two patches on the patient's back which was poisoning the patient according to the reporter and which would be 4 days with the problems. The patient found something that made her sick to her stomach. On 17 Jun 2010 the patient had illegal IV inserted. On (b) (6) the **patient was hospitalized and was very dehydrated, vomiting, shaking and had tremors.** The patient had low blood pressure and looked very weird. On (b) (6) the patient was hospitalized from vomiting green bile. On (b) (6) the patient was hospitalized for unknown reason. On 05 Feb 2011 the patient was double patched and the patch was on elbow. On 09 Feb 2011 the patient was in physical therapy and was staring into space and she 'reeked of bowel movement'. On (b) (6) the patient was hospitalized for as she was dehydrated and had major urinary tract infection. On 04 Mar 2011 the patient had urine spin since she had a major urinary tract infection. The patient received 14 shots of Gentamicin. On 27 Mar 2011 the patient was throwing up. The patient was absolutely raw in her diaper area. On 06 May 2011 the patient was patched on the left upper arm and again on 08 May 2011 patched in the same area**. The reporter stated that the patient was double patched two days before she had brain hemorrhage.** The reporter further mentioned that the patient's leg was torn and also the patient had difficulty in passing stool. The reporter also noticed bruise on her hand and a cut on her leg. **It was reported that the dose of Exelon was doubled.** The reporter was concerned about the patient's health and stated that her mother's life was on the line. The physician's staff on 16 May 2011 reported that the patient had no adverse events and no signs and symptoms were noted. The final outcome and causality of the event was not reported.Follow up received from consumer (patient's daughter) on 05 Apr 2011: The description of the event was added, new events added.Follow up received from consumer (patient's daughter) on 19 Apr 2011: The description of the event was added.Combined follow up report received from consumer (patient's daughter) on 19 Apr 2011 and 20 Apr 2011: The description of the event was added.Follow-up report received from a consumer on 28 Apr 2011. Concomitant medications, events, and description of the events in narrative were updated.Combined follow-up report received from consumer on 04 May 2011 and 09 May 2011. Updated narrative information and events.Combined follow up received from consumer on 16 May 2011: Event description was added. Added Medicus number.Follow up report received from the physician's staff on 29 Jun 2011: The physicians staff's comment was added.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
7617988-8	Dose Omission	Improper Dose	Not able to walk, severe dehydration	Case number PHHY2011US61474 is an initial spontaneous report received from a consumer (patient's daughter) on 08 Jul 2011. This report refers to an elderly female patient. Concomitant medications included Namanda 10 mg and Lisinopril 2.5 mg for blood pressure. The patient received Exelon Patch (rivastigmine) for an unspecified indication since an unspecified date. **The patient was without patch for ten days and then back on it without the physician knowing.** The patient was acting different within those ten days. The reporter wanted to know if it could do permanent damage to nerves. It was reported that, the **patient started had overdose on the patch and was not able to walk**. **The patient used 2 or 3 patch on at one time**. On an unknown date, the patient had a urinary tract infection which was untreated and almost went septive. The patient also had severe dehydration. On an unknown date, the patient was in hospital and was in rehab facility. The outcome of the event was not reported.
7691424-8	Improper Dose		Low blood sugar	Case number PHEH2011US01323, is an initial spontaneous repot from a nurse received on 11 Aug 2011. This report refers to a patient whose age and gender was not reported. The patient received Exelon patch (rivastigmine) for an unspecified indication since an unknown date. On an unspecified date, the patient was hospitalized with low blood sugar. **The patient had a patch on for 7 days along with a new patch applied daily**. The action taken with the treatment of Exelon patch, event outcome and causality were not reported.
7691432-7	Improper Dose	Overdose	Collapsed	Case number PHEH2011US01361 is an initial spontaneous report received from a pharmacist on 11 Aug 2011. This report refers to a patient of unknown age. This patient's current condition included diabetes. The patient was on treatment with Exelon (rivastigmine) patch for an unknown indication, since an unknown date. It was reported that **a nurse applied the Exelon patch to a patient without removing the previous one.** The patient was subsequently discharged and later collapsed. As the patient was also diabetic, the nurse was trying to find out if the Exelon patch medication error could have been the cause of this event. The pharmacist also inquired whether any residual drug was left in the patch. The events outcome was not reported.
7725671-3	Improper Dose	Overdose	Nauseous	Case number PHEH2011US02846 is an initial spontaneous report received from a health care professional (nurse) on 23 Aug 2011. This report refers to a female patient of an unknown age. The patient received Exelon Patch (rivastigmine) for an unspecified indication on unspecified date. On unknown date, **the patient had applied three patches on her at one time. The patient became very nauseous and sick. The patient was hospitalized for the events. Once the patches were removed symptoms resided and then resolved.** On an unspecified date, the patient went back to long term care facility. The outcome of the event was reported as complete recovery.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
7775386-0	Improper Dose, Wrong Prescribing	PQI	Tired, depressed, losing weight; sensitivity, itching	Case number PHEH2011US03412 is combined initial spontaneous reports received from consumer on 06 Sep 2011 and 07 Sep 2011 with combined follow up report received from a consumer on 15 Sep 2011 and 19 Sep 2011. This report refers to a 65-years-old polymedicated female patient. The concurrent condition included thyroid (unspecified), anxiety, seizures, cholesterol and osteoporosis. The patient started Exelon patch (rivastigmine) 4.6 mg transdermally for unspecified indication since 2 months ago (date unspecified). On an unspecified date, the patient stated that she did not know if she had "Alzheimer's" but experienced a lot of dementia and she felt like she can't do anything. She also had seizures (couple of times) and received medication (unspecified) due to this, but mostly takes it because of impending doom feeling. The patient was tired before using Exelon patch, but it was overwhelming now. The treatment was discontinued for 3 weeks because she thought that patch was not working. After the doctor's advice the patient started to receive the Exelon patch. **The patient reported that she was using her nails to scratch of the circle of adhesive left on her skin after taking the patch off. The patient also used alcohol to get it off of her back, and it made her back red. The arms were full of the adhesive circles. About 2 or 3 weeks ago, she also forgot to take one patch off before putting on a new one. In follow up it was reported that the patient's Exelon patch dose was increased to 9.5mg at 1 patch per day. As there was a leftover of Exelon patch 4.6mg, the doctor advised her to apply 2 patches which would be of equal the dosage.** The patient experienced sensitivity and itchiness, so she was wondering if it was where she had applied the patch. On an unspecified date, patient experienced serious depression and losing weight. The nurse said to stop taking this until the symptoms go away. The patient on 9.5mg and she said to stop the medication but she wanted to make sure it was okay to stop taking it gradually. The outcome of the events was not reported. Combined Follow up report received from a consumer on 15 Sep 2011 and 19 Sep 2011. Added concomitant medication and condition and events.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
7785443-0	Improper Dose	Overdose	Nausea, vomiting	Case number PHEH2011US02661, is a spontaneous report initially received from a nurse on 26 Aug 2011, with follow up report from consumer on 29 Aug 2011, from physician on 31 Aug 2011, from a consumer on 30 Aug 2011 and from the physician on 20 Sep 2011. This report refers to a 77-years-old male patient. The patient had medical history of depression, anxiety and chronic urinary tract infection. The patient's concomitant medication included Celexa (citalopram hydrobromide), Lasix (furosemide), Bactrim ds (sulfamethoxazole, trimethoprim), and Xanax (alprazolam) .The patient started Exelon patch (rivastigmine) for an unknown dose for dementia on an unspecified date. The patient had been on Exelon Patch 4.6 mg for approximately 30 days. The patient switched to the higher dose 9.5 mg on 08 Jul 2011. **For a period of 5 days, the nursing home placed a new patch without removing patch from the previous day. By the fifth day the patient was very sick and had to be hospitalized. On an unspecified date, the patient had overdose due to application of 6 of the 9.5 mg patches on at the same time On 12 Aug 2011, the patient experienced nausea and vomiting. The patient was taken to the emergency room and diagnosed with urinary tract infection. Also on 12 Aug 2011 the patient was found with 5 Exelon patches on body.** The patient was not feeling well. The patient was taken to the emergency room, no cardiac adverse effects, atropine was not used. Because of UTI (urinary tract infection) history the patient was started on Ceftin (cefuroxime axetil) 250 mg, no culture was done. The outcome for the event nausea and vomiting was reported as recovered on 16 Aug 2011. Outcome of other events were improved. The physician assessed the events nausea and vomiting as non serious. The physician assessed the casualty of the events nausea and vomiting as not related to Exelon Patch. Reporter wanted information on incidence of urinary tract information and Exelon overdose since the patient had 6 of the 9.5 mg patches on the same day. The consumer wanted information on transdermal system application. The physician enquired about the total amount of drug contained in the 9.5 mg Exelon Patch. He also wanted to know if an overdose of Exelon Patch could cause a urinary tract infection.Combined follow up report received on 29 Aug 2011 and 31 Aug 2011: Narrative updatedFollow up received from a consumer on 30 Aug 2011: Added suspect product information and new event.
7929830-6	Improper Dose	Overdose	Hospitalized	Case number PHEH2011US009480, is an initial spontaneous report from a physician received on 14 Nov 2011. The report refers to a female patient of unknown age. The patient received Exelon (rivastigmine) trans therapeutic system patch for the treatment of unknown indication at unknown daily dose. On an unspecified date the **patient applied six patches on her body and then hospitalized.** The reporter informed that patient was better now. Action taken to Exelon patch was unknown. The event was considered serious (hospitalization) by the physician. The event causality was unknown.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
7937786-5	Improper Dose	Wrong Drug	delusions, hallucinations, frightening bad dreams, and dizziness. itching on the inner forearms and lower legs	Case number PHEH2011US04509, is an initial spontaneous report from a consumer (patient's wife) received on 15 Sep 2011 with follow up received from quality assurance on 15 Oct 2011. This is also a quality complaint (278332, 278342, 280599, and 280602). This report refers to a 79-year-old male patient. The wife reported that it is not known if her husband had Alzheimer's disease. This polymedicated patient received Exelon patch (rivastigmine) trans therapeutic system for the treatment of unknown indication from in Feb 2011 or Mar 2011 at a dose of 4.6mg/24 Hrs. The patches were used for 1 to 3 months then the patient switched to the Exelon patch 9.5mg/24 Hrs. The patient's wife stated that there was **adhesive left on the patient's skin after each Exelon patch (4.6 mg and 9.5 mg).** On an unspecified date, **he ran out of the 30 days' supply of the Exelon patch 9.5mg/25 Hrs and could not get the patches locally; the patient took 1 Exelon (rivastigmine) capsule in the morning on an unknown date. The patient began to experience delusions, hallucinations, frightening bad dreams, and dizziness and could hardly get up about 12 hours later. The patient had to lie down on a couch. He stopped taking Exelon capsule immediately. The next day, the reporter began to apply 2 Exelon Patches 4.6mg/24 Hrs on the patient's skin. The patient continued to use the 2 Exelon Patch 4.6mg until a 90 day supply of the Exelon Patch 9.5mg/24 Hrs was gotten. The patient experienced itching on the inner forearms and lower legs. The legs and arms also swelled up. The patient could barely get his wedding ring off. The itching went away and the swelling went down. The patient's left hand then started to peel.** A doctor at the church told the patient's wife to stop the patches, but they were not stopped. The outcome of itching was reported as itching went away and of swelling it was reported as swelling went down. The outcome of other events was not reported. The final complaint justification report confirmed that, no testing required, and no other complaints of this nature received for the lot, the reported lack of effect could not be attributed to a product quality issue.Follow up received report received from quality assurance on 15 Oct 2011: Updated quality investigation summary report.
8114084-0	Improper Dose	Overdose	cholinergic crisis and the patient experienced abdominal pain, nausea and vomiting	Initial physician report received on 21 Jan 2011: This patient was treated with Exelon patch 9.5 mg (rivastigmine) for mild to moderate Alzheimer's disease since an unspecified date. On 13 Jan 2011, **the patient placed 10 Exelon patches on her body which led to a cholinergic crisis and the patient experienced abdominal pain, nausea and vomiting. The patient went to emergency room where treatment with atropine and IV fluids was given to the patient.** The symptoms got resolved on 14 Jan 2011.Following an internal review on 01 Feb 2012 for the case with MRD on 21 Jan 2011 a significant correction was done, where the event coding was changed from wrong technique in drug usage process to incorrect dose administered.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
8126504-6	Improper Dose	Overdose	respiratory depression resulting in hospitalizatio n	Initial report received from a pharmacist on 22 Jun 2010: This patient was treated with Exelon patch 4.6 mg (rivastigmine) for an unknown indication since an unknown date. On an unspecified date, **the patient was given multiple patches (4 patches of 4.6 mg were applied). When the nurse realized it, she removed three patches and kept one. The following midnight, the patient experienced respiratory depression resulting in hospitalization.** The patient was placed on vent. The reporter stated that the patient was doing well. The doctors at hospital believed that hospitalization was not caused by Exelon.Following an internal review on 01 Feb 2012 for the case with MRD on 22 Jun 2010 a significant correction was done, where the event coding was changed from wrong technique in drug usage process to incorrect dose administered.
8154825-X	Improper Dose		None Reported	Case number PHEH2012US002883, is an initial spontaneous report received from consumer on 02 Feb 2012 with combined follow up from a consumer both reports received on 13 Feb 2012. This case refers to 75-year-old male patient. The patient had current condition of high blood pressure and was on medication (unspecified). This poly medicated patient received Exelon (rivastigmine) at the dose of 4.6mg daily for an unknown indication since seven weeks. The reporter stated that her husband was on the samples of Exelon patch when he had kidney stones. On (b) (6), the patient was hospitalized to have surgery for kidney stone removal. The **patient went on with an Exelon Patch on, and when he was released the same day, she couldn't find the patch anywhere and thought someone from the hospital removed it. She just put a new patch on. After that the patient finally found the patch that she thought the hospital removed and took it off. He was been wearing 2 patches for five days now since his wife forgot where she placed the patch on him before he was in the hospital.** Outcome of the event was unknown.Combined follow up from a consumer both reports received on 13 Feb 2012: Added concomitant medications, new event (kidney stone), and information on clinical course of the event.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
8168108-5	Improper Dose		No ADR	Case number PHHO2011US05149, is a report received from clinical study ENA713DUS44. This 83-year-old female subject (centre number 648, patient number 9) was enrolled in a 24 week, prospective, randomised, parallel-group, double-blind, multicentre study comparing the effects of Rivastigmine patch 15 cm2 vs. rivastigmine patch 5 cm2 on activities of daily living and cognition in patients with severe dementia of the Alzheimer's type. The subject's medical history included hearing impairment, cerebrovascular event in the left temporal region, major depression, hypothyroidism, encephalomalacia in the left temporal region, hypercholesterolaemia, basal cell carcinoma of the neck, basal cell carcinoma excision, hypertension, allergy to penicillin, agitation, aortic valve sclerosis, chronic obstructive pulmonary disease (COPD), bronchiectasis, pneumonia, breast cancer, breast cancer excision, arthritis of the knees, osteoporosis, hayfever, allergy to PCN, vitamin B12 deficiency, mild myasthenia gravis and bronchitis. The subject's concomitant medications included simvastatin, azathioprine, levothyroxine, Pristiq, Fosamax and losartan with hydrochlorothiazide. The subject started study medication on 08 Mar 2011.On 11 Mar 2011, 4 days after starting study medication, the subject's caregiver contacted the investigator and reported that the **subject had an extra Exelon patch applied to their body (The subject's caregivers are responsible for the application of the study medication patches, a requirement for the subject's participation in the study). When applying the Exelon patch, at 13:30, it was discovered that the subject had three patches already applied to her body.** These three patches were removed immediately. The caregivers assured the investigator that the patient was stable and asymptomatic. It was determined that one Exelon patch was applied on 10 Mar 2011 as per the protocol but was not removed after 24 hours or before another two patches were applied. The specific time of application of the first patch was not known. No active study medication was expected to have been released from this patch after the initial 24 hours. The investigator stated the **caregivers had not followed the instructions to keep the study medication in their possession and had instead stored the medication in the subject's home. It was therefore likely that the subject's elderly husband applied the two extra patches without removing the previous patch**. On 11 Mar 2011, the study medication was interrupted. The investigator instructed the subject's caregivers to contact him if there were any changes in the subject's condition and to not resume any active treatment until they had spoken to him on 14 Mar 2011. The final outcome of the event was reported as complete recovery on 11 Mar 2011. On 14 Mar 2011, the subject was still asymptomatic with a pulse rate of 100 beats per minute. Study medication was re-started that day (14 Mar 2011). The investigator stated this pulse rate was similar to the subject's baseline rate. The subject's caregivers assured the investigator they would be holding the study medication and would assume full responsibility for the application of the patches. The event was considered medically significant by the investigator. The investigator reported the event was not due to a lack of efficacy or progression of underlying disease. The subject received last dose of

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
				study medication (end of study) on 03 Sep 2011. The investigator suspected the event to be related to the study medication.Case correction following internal review on 06 Apr 2011: Additional study medication tab added.Follow-up received on 21 Apr 2011: Added date study medication was re-started.Follow up data reconciliation report received on 20 Feb 2012: Study medication details (end of study medication date) were updated.Following an internal review performed on 22 Feb 2012, the following correction was done: Study medication restart was added in the product details.
8101764-6	Overdose		visual hallucination, myalgias and diarrhea	Case number PHEH2012US000620 is an initial spontaneous report received from consumer on 05 Jan 2012 with follow up report received from a consumer and physician on 23 Jan 2012: This report refers to 82 year old male patient. The patient was previously treated with Cerefolin ACE, prescribed by another doctor. This poly medicated patient received Exelon patch (rivastigmine) for an unknown indication at a dose of 4.6 mg per day. On an unspecified date **the patient's dose was increased to 9.5 mg per day (batch number: 1601 A). On an unspecified date, the patient lost all what was going on him, lost control on his bowels and lost control on his hands and legs. The patient had horrible illusions, nightmares and lost all his short term memory. It was reported that, the patient could not remember how to get out of bedroom. It stated that when watching TV, he would fall asleep for 30-60 minutes and when he would wake up; he thought it was a different time of the day and thought he was late for work. The patient could not remember the date. The patient used 2 patches of Exelon but the second patch was removed before the full 24 hours**. On an unspecified date, the patient also experienced visual hallucination, myalgias and diarrhea. The patient discontinued Exelon 9.5 mg patch after only one and half days worth. The physician advised patient back to 4.6 mg per day of the Exelon patch. The outcome of the events were reported as the patient has fully improved and not reported for hallucination, myalgias and diarrhea. The causality of the events was not reported. Follow up report received from a consumer and physician on 23 Jan 2012: Added events visual hallucination, myalgias, diarrhea, narrative and outcome of the events were updated.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
8114079-7	Wrong Route of Administration	Overdose	agitated, restless. Stable vital signs	Initial consumer report received from patient on 11 Oct 2010: This patient was on treatment with Exelon (rivastigmine) trans therapeutic system patch for unknown indication with unknown dose since an unknown date. It was reported that, **the patient ate an Exelon patch and had experienced good effect who monitored for cardiac issues.** The outcome of event was unknown. No other information was available.Follow-up report received from a physician on (b) (6) It was reported that this polymedicated patient with historical condition of dementia of mixed type including Alzheimer's, Lewy body dementia, parkinsonism, migraine, atypical chest pain and status post hysterectomy. The patient received treatment with Namenda (memantine hydrochloride) and Exelon patch and was presented to the emergency room for concern of Exelon patch ingestion. **It was reported that the ingestion occurred one hour prior (at about 10:30 am) to arrival in emergency room. The patient was upset in the emergency room and had become agitated at the thought of admission. The patient received charcoal and whole-bowel irrigation with Golytely, which was tolerated well. The patient's vitals were stable with no evidence of anticholinergic side effects. It was reported that the patch contain 10 times the amount of drug to be used as transdermal effectively hence the concern was that she ingested about 95 mg rivastigmine**. After admission in the hospital the patient's vital sign was reported as blood pressure 114/65, heart rate 76, respiratory rate 14 and oxygen saturation 98 % with normal laboratory reports. The physical examination showed that she was agitated, restless and was trying to get out of the stretcher. The psychiatric condition was reported as judgement and insight impaired, orientation was significantly impaired, mood and affect were agitated, and memory was impaired. The patient was stable and recommended to hold Exelon and Namenda. The patient was discharged (date unknown) with a diagnosis of Exelon overdose. The events outcome was not reported.Following an internal review on 01 Feb 2012 for the case with MRD on (b) (6) a significant correction was done, where the event coding was changed from wrong technique in drug usage process to incorrect route of drug administration.

ISR Number	Type of Error 1	Type of Error 2	Outcome	Narratives
6980541-3	Wrong Technique		None Reported	Initial report received from a consumer on 28 Jul 2010: This polymedicated patient was on treatment with Exelon patch (rivastigmine) at a dose of 9.5 mg from an unknown date for an unspecified indication. **Patient enquired that if it was alright for him to cut the Exelon patch into two.** The patient was prescribed with 9.5 mg patch and he discovered that he was having very loose bowel movements; he stated that it totally changed his bowel movement. He reported that he had to get up at night and rush to the comfort room and he had 4 to 6 bowel movements a day. His doctor gave him samples of Exelon patch of dose 4.6 mg which he used for about 10 days and noticed that the symptoms subsided. He reported that at the time of the report, he had undergone a surgery for his urinal tract problem and they had to remove a scar tissue. **The reporter stated that he only had the 9.5 mg patch left and he had it cut in half since he did not want to have a bowel movement problem while undergoing his surgery.** Doctors details were provided. The outcome was reported to be unknown.Follow-up report received from treating physician on 03 Sep 2010: The patient presented with diarrhoea after treatment with Exelon 9.5 mg patch which was assessed as medically significant by the reporting physician. As measure, Exelon patch 4.5 mg was started and the patient remained asymptomatic on Exelon 4.6 mg patch. The reporter further stated that the patient continued to take 4.6 mg patch.

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/s/

JUNG E LEE
06/26/2012

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06/26/2012

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	June 15, 2012
Reviewer(s):	Reema Mehta, PharmD, MPH, Sr. Risk Management Analyst Division of Risk Management
Team Leader:	Kendra Worthy, PharmD, Team Leader Division of Risk Management
Division Director	Claudia Manzo, PharmD, Director Division of Risk Management
Drug Name(s):	Exelon® (rivastigmine)
Dosage form and Route:	transdermal patch
Application Type/Number:	NDA 22-083
Applicant/sponsor:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2011-4277

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CONTENTS

1 INTRODUCTION

This memorandum documents the review by the Division of Risk Management (DRISK) to review the proposed risk management plan submitted by Novartis Pharmaceuticals Corporation for Exelon® (rivastigmine) for the supplement, submitted on October 31, 2011, for a new dosage strength for the transdermal formulation. The currently approved transdermal Exelon patch does not have an approved Risk Evaluation and Mitigation Strategy (REMS).

1.1 BACKGROUND

Exelon (rivastigmine), a reversible cholinesterase inhibitor, is approved for the treatment of mild to moderate dementia of the Alzheimer's type and Parkinson's disease. It is postulated that rivastigmine enhances cholinergic function by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. The effect of rivastigmine may lessen over time as the disease advances and fewer cholinergic neurons remain fully intact.

Exelon is currently available as an oral solution, capsule, and transdermal patch. The transdermal patch is available as a matrix patch in the following dosage strengths: 5 cm^2 patch containing 9 mg rivastigmine base with *in-vivo* release rate of 4.6 mg/24 hours and 10 cm^2 patch containing 18 mg rivastigmine base with *in-vivo* release rate of 9.5 mg/24 hours. Treatment is started with Exelon patch 4.6 mg/24 hours and can be increased to 9.5 mg/24 hours patch after at least 4 weeks if well tolerated. The recommended effective dose is 9.5 mg/24 hours.

1.2 REGULATORY HISTORY

Exelon was initially approved on April 21, 2000 for the oral solution and capsule dosage forms. On July 6, 2007, Exelon was approved for the transdermal matrix patch formulation (4.6 mg/24 hours and 9.5 mg/24 hours). Exelon does not have an approved REMS.

On October, 31, 2011, Novartis submitted a supplemental NDA for NDA 22-083 Exelon patch to obtain approval for a new dosage strength of the transdermal formulation. The proposed formulation is a 15 cm^2 patch containing 27 mg rivastigmine base with *in-vivo* release rate of 13.3 mg/24 hours for use in the currently approved indications.

2 MATERIALS REVIEWED

- Novartis Pharmaceuticals Corporation Safety Risk Management Plan for Rivastigmine, submitted October 31, 2011.
- Internal Meeting Minutes for Mid-cycle Meeting for Exelon patch sNDA 22-083, dated April 3, 2012.
- Novartis Pharmaceuticals Corporation Prescribing Information for Exelon® (rivastigmine), approved August 27, 2010.

3 RESULTS OF REVIEW OF NEED FOR RISK EVALUATION AND MITIGATION STRATEGY FOR EXELON TRANSDERMAL PATCH

3.1 SPONSOR'S SUBMISSION

The submission included Study CENA713D2340 (Study D2340) with the intent to seek approval of the Exelon 15 cm^2 patch (13.3 mg/24 hours) in patients with mild to moderate Alzheimer's disease. Study D2340 was a 48-week, multi-center, randomized, double-blind, parallel group evaluation of the comparative efficacy, safety, and tolerability of Exelon 10 cm^2 and 15 cm^2 patches in patients with Alzheimer's Disease showing cognitive and functional decline while being treated with Exelon 10 cm^2 patch during an initial 26-48 week open-label treatment phase.

The sponsor also included a Safety Risk Management Plan in the submission that utilizes the European format for risk management plans. The safety specification in the sponsor's submission includes the following identified and potential risks for the transdermal patch.

Identified risks:

- Gastrointestinal symptoms (nausea, vomiting, and diarrhea
- Worsening of motor symptoms associated with Parkinson's disease
- Pancreatitis
- Cardiac arrhythmias
- Exacerbations of asthma and COPD
- Application site skin reactions and irritations
- Hypertension
- Gastrointestinal ulceration, hemorrhage, and perforation
- Seizures
- Hallucinations
- Syncope and loss of consciousness
- Medication misuse
- Medication errors
- Dehydration
- Liver disorders

Potential risks:

- Severe skin reactions (bullous reactions)
- Myocardial infarction
- Cerebrovascular accident
- Pulmonary infections
- Death
- Acute renal failure

3.2 SPONSOR'S RISK MANAGEMENT PROPOSAL

The sponsor's risk management plan addresses the identified and potential risks above through routine pharmacovigilance and product labeling. The sponsor did not propose any additional risk mitigation activities for the aforementioned risks cited in Section 3.1.

4 DISCUSSION AND CONCLUSION

DRISK believes the proposed routine approach by the sponsor is adequate at this time. Should DNP raise further concerns with the risks outlined above or identify additional risks associated with Exelon warranting more extensive risk mitigation or a formal REMS, please send a consult to OSE DRISK.

This memo serves to close the existing consult request for the efficacy supplement for Exelon under NDA 22-083. Please notify DRISK if you have any questions.

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/s/

REEMA J MEHTA
06/15/2012

CLAUDIA B MANZO
06/15/2012
concur

DSI CONSULT: Request for Clinical Inspections

Date: January 20, 2012

To:

Tejashri Purohit-Sheth, M.D., Acting Division Director
Susan Thompson, M.D. Acting Team Leader
Antoine El-Hage, Ph.D, Clinical Reviewer
Office of Scientific Investigations
Office of Compliance/CDER

Through: Nicholas Kozauer, MD – Clinical Reviewer
Russell Katz, MD - Director
Division of Neurology Products

From: Teresa Wheelous, Sr. Regulatory Health Project Manager / Division of Neurology Products

Subject: **Request for Clinical Site Inspections**

I. General Information

Supplement # NDA-22-083/S-016
Applicant/ Applicant contact information (to include phone/email):
Drug Proprietary Name:
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): a new dosage strength of the transdermal formulation (13.3 mg/24 hours nominal release rate, 27 mg total drug load, 15cm2 patch size) for use in the currently approved indications for the treatment of mild to moderate dementia of the Alzheimer's type and for the treatment of mild to moderate dementia associated with Parkinson's disease

PDUFA: August 30, 2012
Action Goal Date: August 23, 2012
Inspection Summary Goal Date: July 23, 2012

II. Protocol/Site Identification

Study number: Study CENA713D2340, EUDRACT number 2007-000213-11
Title of study: A 48-week, multicenter, randomized, double-blind, parallel group evaluation of the comparative efficacy, safety, and tolerability of Exelon® 10 and 15 cm2 patch in patients with Alzheimer's disease showing cognitive decline during an initial open label phase

\\cdsesub1\EVSPROD\NDA022083\\0046\m5\53-clin-stud-rep\535-rep-effic-safety-stud\dementia---alzheimers-type\5351-stud-rep-contr\ena713d2340\ena713d2340--legacy-clinical-study-report.pdf

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Center 307 Dr. Hermann-Josef Gertz PI Arneimittelforschung Leipzig GmbH Paul- Gruner Str. 63 Leipzig 04103 Germany PH: 0341-97 24 420 Fax: 0341-9724-539 E-mail: Hermann-Josef.Gertz@uniklinik-leipzig.de	CENA713 D2340	10 of the 567 total in DB treatment phase	Mild to moderate Alzheimer's disease
Center 318 Dr. Juergen Deckert Klinik der Universitat Wurzburg Fuechsleinstr. 15 Wurzburg 97080 Germany Ph: 0931/201-77000 Fax; 0931/201-77020 E-mail: Deckert_J@klink.uni-wuerzburg.de	CENA713 D2340	6 of the 567 total in DB treatment phase	Mild to moderate Alzheimer's disease

U.S. Authorized Contact Info: **Peter McArdle, DVM**
Director, Drug Regulatory Affairs
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 778 3228
Fax +1 973 781 3310
Cell +1 862 926 9555
peter.mcardle@novartis.com
www.novartis.com

III. Site Selection/Rationale

First, I tried to see if there is any influential center by taking out each of the centers with more than 5 patients from the primary efficacy analysis, for both ADAS-COG and ADCS-ADL, separately. No suspicious center is identified.

Second, since country seems like a significant effect in the model, I tried to see if there is any influential country by taking out each of the country from the primary efficacy analysis, for both ADAS-COG and ADCS-ADL, separately. In this way, I found the impact of Germany on the results is fairly large. Without Germany, the p-value for ADAS-cog is changed from 0.23 to 0.73 and the p-value for ADCS-ADL is changed from 0.0002 to 0.012. The patients from Germany are only 13% of the total population (72/536). Thus, if we need to do investigation, I would like to recommend investigating a few largest centers in Germany. Below is a list of centers in Germany with more than 5 patients (note: center information is missing for some patients).

Center	Frequency	Percent
307	10	16.95
318	6	10.17
327	6	10.17
319	5	8.47
326	5	8.47
328	5	8.47

Rationale for DSI Audits
See above

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
_x__ 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) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Teresa Wheelous at *301-796-1161 or Nicholas Kozauer* at 301-796-2250.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
Russell G. Katz, MD_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

****Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*

- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/

TERESA A WHEELOUS
01/20/2012

RUSSELL G KATZ
01/25/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-083/S016

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22083 SUPPL # 016 HFD # 120

Trade Name Exelon Patch 13.3 mg/ 24 hr

Generic Name rivastigmine

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known 8/31/12

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

(b)(1) - SE2 increase in daily dosage

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 ☐

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:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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 ☐

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

NDA# 22083 Exelon Patch

NDA# 20823 Exelon Capsules

NDA# 21025 Exelon Oral Solution

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 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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 ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 8:

(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 ENA713D2340 (D2340)]

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 ☐

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

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 ☐

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

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 1: Study ENA713D2340 (D2340)

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 # 54051	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 ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! 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:

==========

Name of person completing form: Teresa Wheelous
Title: Sr. Regulatory Mangement Officer
Date: 9/11/12

Name of Office/Division Director signing form: Russell Katz, MD
Title: Director, Division of Neurology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

TERESA A WHEELOUS
09/14/2012

ERIC P BASTINGS on behalf of RUSSELL G KATZ
09/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 22083/S-016

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Novartis Pharmaceuticals Corporation
Attention: Peter D. McArdle, DVM
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. McArdle:

We have received your October 31, 2011, Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 22083

SUPPLEMENT NUMBER: 016

PRODUCT NAME: Exelon® Patch (rivastigmine transdermal system)
13.3 mg/24 hours

DATE OF SUBMISSION: OCTOBER 31, 2011

DATE OF RECEIPT: OCTOBER 31, 2011

This supplemental application proposes the following changes:

- a new dosage strength of the transdermal formulation (13.3 mg/24 hours nominal release rate, 27 mg total drug load, 15cm2 patch size) for use in the currently approved indications for the treatment of mild to moderate dementia of the Alzheimer's type (AD)
- and for the treatment of mild to moderate dementia associated with Parkinson's disease (PDD)

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 December 30, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under

21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Teresa Wheelous, R. Ph.
Sr. Regulatory Management Officer
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

TERESA A WHEELOUS
12/27/2011

From: Wheelous, Teresa A
Sent: Thursday, August 16, 2012 1:30 PM
To: Materna, Joan; McArdle, Peter
Subject: NDA 22083-S016 Agency Comments Prior to 8/16/12 Telecon

Importance: High

Attachments: Exelon (b) (4) Comments.doc

Joan and Peter,

We have the following information to communicate prior to today's CMC conference regarding the Release Liner (b) (4):

The acceptance criterion for the peel from release liner specification does not reflect the updated stability data that was provided on 15-AUG-2012 utilizing (b) (4) release liner. Based on the data, we recommend revising the acceptance criterion for all proposed strengths of the drug product.

Additionally, the following and the attached are the Agency's preliminary response to your proposed (b) (4) specification and acceptance criterion:

Exelon (b) (4) Comments.doc ...

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TERESA A WHEELOUS
08/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22083/ S-016 **LABELING PMR/PMC DISCUSSION COMMENTS**

Novartis Pharmaceuticals Corporation
Attention: Peter D. McArdle, DVM
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. McArdle:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 31,2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exelon® Patch (rivastigmine transdermal system) 13.3 mg/24 hours.

We also refer to our January 8, 2012, letter in which we notified you of our target date of August 11, 2012 for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On February 14, 2012, we received your February 14, 2012 proposed labeling submission to this application, and have proposed revisions which are included as an enclosure. These revisions have been reviewed and cleared to the level of Cross Discipline Team Leader

Division of Medication Error Prevention and Analysis Comments

A. Carton Labeling
1. Medication errors associated with wrong route of administration have been reported in post-marketing use. Relocate the route of administration statement, "For Transdermal Use Only", which is currently on the back panel of the carton labeling and pouch label to the principal display panel directly below the statement of strength to reinforce the proper route of administration for this product. Additionally, we recommend this labeling revision be implemented on the 4.6 mg/24 hours and 9.5 mg/24 hours carton labeling at the time of the next printing.

B. Foil Pouch Label
1. Include the statement "Change the location of each new patch" on the back panel of the foil pouch label following the statement "Apply patch to intact skin immediately after removal from pouch". To allow space for this statement, relocate the route of administration statement to the principal display panel (See Comment A1 above). Additionally, we recommend this labeling

revision be implemented on the 4.6 mg/24 hours and 9.5 mg/24 hours foil pouch labeling at the time of the next printing.

We remind you that a final decision about the approvability of this application (the efficacy supplement for the 13.3 mg/24 hour Exelon® patch) has not yet been made. If you have any questions, call me at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Teresa Wheelous, R. Ph.
Sr. Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

TERESA A WHEELOUS
07/24/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Patient Labeling Team. Contact for PLT: Carol McAlman or Chris Wheeler	FROM (*Name, Office/Division, and Phone Number of Requestor)*: ODEI / Division of Neurology Products/ Teresa Wheelous/ 301-796-1161

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/18/11		22083 S-016	sNDA - PPIFU	October 28, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Exelon Patch 13.3 mg/ 24 hr	Standard		July 14, 2012

NAME OF FIRM: Novartis Pharmaceuticals Corporation

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Novartis has submitted a new strength of an approved product, Exelon Patch, which includes a PPIFU. I have attached a copy of the email from Carol McAlman. The following is the electronic link information to the submissionCover Letter: \\CDSESUB1\EVSPROD\NDA022083\0046\m1\us\cover.pdf
EDR Location: \\CDSESUB1\EVSPROD\NDA022083\0046

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Teresa Wheelous 301-796-1161	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

From: McAlman, Carol
To: Wheelous, Teresa A;
cc: McAlman, Carol;
Subject: FW: sNDA 22083-Patient Labeling Consult
Date: Tuesday, November 15, 2011 2:42:27 PM

Good Afternoon,
OSE informed us of the below sNDA and it may contain Patient Labeling. We reviewed the submission and it contains a PPI/IFU that the Patient Labeling Team will review. The Patient Labeling Team is no longer part of OSE, so could you please send a formal consult via DARRTS so that we can attach the completed review? Please also let us know when the labeling is substantially complete as our review will be completed about 14 days from that point. Please contact me if you have any questions.

Thanks,
Carol

Carol A. McAlman, Project Manager
LCDR, U.S. Public Health Service
Office of Medical Policy Initiatives/Division of Medical Policy Programs
10903 New Hampshire Ave.
Building 51, Room 2214
Silver Spring, MD 20993
Ph: (301) 796-2652
Email: Carol.McAlman@fda.hhs.gov

From: CDER-DMPP-PatientLabelingTeam
Sent: Tuesday, November 15, 2011 2:32 PM
To: McAlman, Carol
Subject: FW: sNDA 22083

From: Dempsey, Mary
Sent: Tuesday, November 15, 2011 10:58 AM
To: Kelley, Laurie

Cc: Shibuya, Robert; Worthy, Kendra; Dempsey, Mary; CDER-DMPP-PatientLabelingTeam
Subject: RE: sNDA 22083

Hi Laurie,

This product was approved in July 2007 with a Patient Package Insert and no additional risk mitigation strategy.
Rivastigmine has been developed for treating patients with mild to moderately severe dementia of the Alzheimer type, also termed probable Alzheimer's disease (AD) or Alzheimer's disease as well as patients with mild to moderately severe dementia associated with Parkinson's disease (PDD).

This response is also forwarded to DMPP because Patient Labeling will need to review the PPI.

DRISK has not previously reviewed this application and I will defer to Kendra on the appropriateness of a DRISK review to verify that the only risk mitigation strategy necessary is the proposed labeling.

Please wait for Kendra's response.

Thanks,

MaryD

From: Kelley, Laurie
Sent: Tuesday, November 15, 2011 10:39 AM
To: Dempsey, Mary
Cc: Shibuya, Robert; Kelley, Laurie
Subject: sNDA 22083

Mary

Novartis has submitted an sNDA for Exelon patch that proposes a new dosage strength. As a part of the submission (made 10/28/11 Suppl 16) they have submitted a "Safety Risk Management Plan" which discusses

their plan for minimizing various risks associated with the product, but is not a "REMS". Before I create an RCM I wanted to let you know that it is there and to make sure that DRISK wishes to review it.

Laurie

Laurie Kelley, PA-C
Safety Regulatory Project Manager
FDA, CDER
Office of Surveillance and Epidemiology
Bldg. 22, Room 4435
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

tel: 301.796.5068

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/s/

TERESA A WHEELOUS
11/18/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO: **CDER-DDMAC-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Teresa Wheelous, Sr. Reg. Management Officer / Division of Neurology Products/ 301-796-1161

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (New strength of an approved product) (PLEASE CHECK OFF BELOW)
8/6/12		2083 / S-016	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Exelon Patch 13.3 mg (new strength)			8/22/12

NAME OF FIRM: Novartis	PDUFA Date:

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply)	TYPE OF APPLICATION/SUBMISSION	REASON FOR LABELING CONSULT
XPACKAGE INSERT (PI) PATIENT PACKAGE INSERT (PPI) ☐ CARTON/CONTAINER LABELING ☐ MEDICATION GUIDE X INSTRUCTIONS FOR USE(IFU)	☐ ORIGINAL NDA/BLA ☐ IND X EFFICACY SUPPLEMENT ☐ SAFETY SUPPLEMENT ☐ LABELING SUPPLEMENT X PLR CONVERSION	☐ INITIAL PROPOSED LABELING XLABELING REVISION

EDR link to submission:
EDR Location: \\CDSESUB1\EVSPROD\NDA022083\0046
Substantially complete label is in eroom http://eroom.fda.gov/eRoom/CDER9/DivisionofNeurologicalProducts/0_13f7c

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Labeling Meetings: [8/15, 8/22, 8/29 M – these are dates are tentative pending the need]
Wrap-Up Meeting: [8/3/12]
A copy of our recent email communications follow.

SIGNATURE OF REQUESTER
Teresa Wheelous

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) X eMAIL ☐ HAND

Hello Theresa,

OPDP (formerly) DDMAC will review this labeling but we need an official consult placed into DARRTS. OPDP should receive consult no later then after the filing meeting. For PLR supplements we need the consult request as soon as the application comes in. Quynh will review this labeling but since she was not including in any milestone meetings it will be challenging for her to complete this by 8/20.

S016 080612
Division 15cm2 lab..

If you have any other questions please do not hesitate to e-mail us anytime.

Thanks,
Olga

From: Wheelous, Teresa A
Sent: Monday, August 06, 2012 12:00 PM
To: DDMACRPM
Cc: Kelley, Laurie
Subject: NDA 22083 S016 Exelon Patch 13.3 mg/hr - Draft Labeling in eRoom

DDMAC,

A link to the Division of Neurology's substantially complete label for Exelon Patch 13.3 mg/24 hours follows for your use and review. I have also attached a WORD version of this labeling.
<< File: S016 080612 Division 15cm2 labeling (clean).doc >>
The PDUFA date for this application is 8/31/12, and your review is requested as close to 8/20/12 as possible.

Please let me know if a formal consult in DARRTS is needed.

Thank you,

Teresa

From: Wheelous, Teresa A
Sent: Monday, August 06, 2012 11:50 AM
To: Mani, Ranjit B; Kozauer, Nicholas; Men, Angela; Dorantes, Angelica; Heimann, Martha R; Freed, Lois M; Parepally, Jagan; Ghosh, Tapash; Dong, Zedong; Tran, Quynh-Van; Thompson, Susan (CDER); Jin, Kun; Kelley, Laurie; Purohit-Sheth, Tejashri; Hulett, Melissa; Williams, Sharon; Scales, Twanda (CDER); Luan, Jingyu (Julia); Freed, Lois M; Hawver, David; Brodsky, Eric
Subject: NDA 22083 S016 Exelon Patch 13.3 mg/hr - Draft Labeling in eRoom

http://eroom.fda.gov/eRoom/CDER9/DivisionofNeurologicalProducts/0_13f7c

Exelon Patch 13.3 mg/24 hr Review Team,

Above is the link to a clean copy of the DNP substantially complete labeling for Exelon patch 13.3mg/hr for your use and edit.

The PDUFA date for this application is 8/31/12, so please add your edits by 8/20/12.

Thank you,

Teresa

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/s/

TERESA A WHEELOUS
08/10/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Vera Viehmann, OPS/ New Drug Microbiology	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Teshara G. Bouie, ONDQA, Division of Post-Marketing Assessment, 301-796-1649

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 17, 2012		22-083	S-016	October 28, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Exelon Patch			May 31, 2012

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☒ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Novartis has submitted an efficacy supplement for a new dosage strength. The microbial limits specifications in the supplement are slightly different from the currently approved strengths. Please review.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Teshara G. Bouie	☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

TESHARA G BOUIE
02/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, OSE, Division of Medical Errors and Prevention, HFD-420

FROM: Teshara G. Bouie, ONDQA, Division of New Drug Quality Assessment I, 301-796-1649

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 17, 2012		22-083	S-016	October 28, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Exelon Patch			May 31, 2012

NAME OF FIRM: Novartis Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The applicant has submitted an efficacy supplement for new dosage strength. Please review carton and container labels. The submission is located in DARRTS.

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Teshara G. Bouie, 301-796-1649	☒ DARRTS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

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/s/

TESHARA G BOUIE
02/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22083/S-016

FILING COMMUNICATION

Novartis Pharmaceuticals Corporation
Attention: Peter D. McArdle, DVM
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. McArdle:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 31,2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Exelon® Patch (rivastigmine transdermal system) 13.3 mg/24 hours.

This supplemental application proposes the following changes:

- a new dosage strength of the transdermal formulation (13.3 mg/24 hours nominal release rate, 27 mg total drug load, 15cm2 patch size) for use in the currently approved indications for the treatment of mild to moderate dementia of the Alzheimer's type and for the treatment of mild to moderate dementia associated with Parkinson's disease

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is August 31, 2012.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 11, 2012.

During our preliminary review of your submitted labeling, we requested, that you submit a revised product label based on the labeling that we provided to you in a December 28, 2011 email communication. We request that you resubmit labeling by February 3, 2012. The resubmitted labeling will be used for further labeling discussions.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Teresa Wheelous, Sr. Regulatory Project Manager, at (301) 796-1161.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

RUSSELL G KATZ
01/08/2012

From:	McArdle, Peter
To:	Wheelous, Teresa A
Subject:	RE: Exelon Labeling Revisions Requested - Oral and transdermal
Date:	Wednesday, December 28, 2011 4:56:11 PM
Sensitivity:	Confidential

Dear Teresa,

Thank you for this note and your directions on what will be required to closeout these outstanding prior approval label supplements for both Exelon Patch (NDA 22083) and Exelon oral formulations (NDA 20823/NDA 21045).

Your directions regarding the Exelon Patch label appear quite straight-forward but I might have to come back to you for further clarification and guidance on what needs to be done to the proposed changes to the label for the oral formulations once I have had the opportunity to review in detail the Division's requested revisions to the patch label and how this will then need to be taken into consideration when preparing the amendment to the pending supplement for the oral formulation that was submitted on 6/2/11.

Thank you Teresa. Novartis is closed for business this week but I will continue to monitor my e-mail and I can also be reached by cell phone if you need to speak with me since I believe the filing date for the $15cm^2$ sNDA is approaching during this period.

Sincerely,
Peter

Peter Mc Ardle, DVM
GPRD
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 7783228
Fax +1 9737818265
peter.mcardle@novartis.com
www.novartis.com

From: Wheelous, Teresa A [mailto:Teresa.Wheelous@fda.hhs.gov]
Sent: Wednesday, December 28, 2011 3:53 PM
To: McArdle, Peter
Subject: Exelon Labeling Revisions Requested - Oral and transdermal
Sensitivity: Confidential

Peter,

I'm in the process of working on the outstanding Exelon (oral and transdermal) labeling supplements, and have the following requests:

Attached you will find a revised version of the approved product label for the Exelon® Patch (NDA 22083). This version contains changes from the currently approved label that are intended to bring the label further into compliance with the Physician's Labeling Rule (PLR) format as well as to more clearly convey the relevant information contained therein. (b) (4)

(b) (4)

We also note that the proposed product labeling that has been included in your 10/31/2011 (S016) supplemental NDA submission for the 15 cm^2 dose of Exelon® Patch builds primarily on the currently approved version of the label for the 10 cm^2 dosage strength. As such, you should also make the appropriate revisions in accordance with the changes to the currently approved version as outlined in this communication. The updated version of the proposed label, with the inclusion of references to the 15 cm^2 dose, could then be submitted to the supplemental NDA for consideration during this review period.

Furthermore, there are several outstanding Prior Approval labeling supplements for the oral formulations product label for Exelon® that have yet to be acted upon by the Division (submitted to both NDA 20823 for the capsule formulation and NDA 21025 for the oral solution). We also note that the 6/25/2009 submission contains a proposed PLR conversion. It is clear, however, that the changes included in the revised version of the Exelon® Patch label attached to this communication will have a significant impact on the proposals made in the outstanding labeling supplements for the oral formulations label. You should therefore submit an updated version of the Exelon® oral formulations label as an amendment to the most recent labeling supplement (dated 6/2/11) to the respective NDAs (22083/21025) with the revised version of the Exelon® Patch label included in this communication serving as a foundation for any of your proposed changes.

Thank you,

Teresa

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/s/

TERESA A WHEELOUS
01/06/2012