Official Title: **A Prospective, 16 Week, Phase IV Study to Evaluate Safety, Tolerability and Effectiveness in Patients With Severe Dementia of the Alzheimer's Type Exposed to Rivastigmine (Exelon)15cm2 Transdermal Patch**

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Clinical Development

Rivastigmine patch

Clinical Trial Protocol CENA713DIN01 / NCT02989402

A prospective, 16 week, phase IV study to evaluate safety, tolerability and effectiveness in patients with severe dementia of the Alzheimer's type exposed to rivastigmine (Exelon) 15 cm^2 transdermal patch

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List of abbreviations

AE	Adverse event
AD	Alzheimer's disease
b.i.d.	twice a day
CMQ	Caregiver Medication Questionnaire
CRF	Case Report/Record Form (paper)
CPO	Country Pharma Organization
CRO	Contract Research Organization
ECG	Electrocardiogram
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
i.v.	Intravenous
IRB	Institutional Review Board
MMSE	Mini-Mental State Examination
o.d.	once a day
p.o.	oral
SAE	serious adverse event

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	The planned stage of the subjects' participation in the study. Each epoch serves a purpose in the study as a whole. Typical epochs are: determination of subject eligibility, wash-out of previous treatments, exposure of subject to treatment or to follow-up on subjects after treatment has ended.
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Subject Number	A number assigned to each patient who enrolls into the study
Part	A subdivision of a single protocol into major design components. These parts often are independent of each other and have different populations or objectives. For example, a single dose design, a multiple dose design that are combined into one protocol, or the same design with different patient populations in each part.
Period	A subdivision of a cross-over study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment	Point/time when patient permanently stops taking

discontinuation	study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Protocol synopsis

Protocol number	CENA713DIN01
Title	A prospective, 16 week, phase IV study to evaluate safety, tolerability and effectiveness in patients with severe dementia of the Alzheimer's type exposed to rivastigmine (Exelon)15cm2 transdermal patch
Brief title	Study of safety and effectiveness of Rivastigmine in Alzheimer patients
Sponsor and Clinical Phase	Novartis
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The present phase IV study is mandated by Indian health authority (HA) as a part of conditional approval to market authorization of rivastigmine 27 mg -15 cm^2 transdermal patch for treatment of severe dementia secondary to Alzheimer's disease (AD). The HA mandated phase IV study in their approval letter. Due to non-availability of Indian data for rivastigmine 27 mg -15 cm^2 transdermal patch in severe dementia secondary to Alzheimer's disease (AD) patients, marketing authorization of the same has been granted condition to phase IV study. As per HA letter, interventional study is to be conducted. Thus the present 16 week study will be conducted to evaluate safety, tolerability and effectiveness in patients with severe dementia of the Alzheimer's type exposed to rivastigmine 27 mg -15 cm^2 transdermal patch as mandated by HA. Most frequent AEs in ACTION study were application site erythema/ dermatitis and UTI, the present study shall assess application site reaction and urine examination.
Primary Objective(s) and Key Secondary Objective	To obtain safety data in patients with severe dementia of the Alzheimer's type treated with rivastigmine 27 mg -15 cm2 transdermal patch for 16 weeks
Secondary Objectives	• To assess patients compliance of rivastigmine 27 mg -15 cm^2 transdermal patch during 16 weeks treatment period

	• To assess the skin tolerability (irritation and adhesion) during 16 weeks treatment period • To assess the proportion of patients with UTI during 16 weeks treatment period • To evaluate treatment effect by rivastigmine 27 mg -15 cm^2 transdermal patch by assessing the changes in Mini-Mental State Examination (MMSE) • To evaluate treatment efficacy by rivastigmine 27 mg -15 cm2 transdermal patch by assessing the changes in ADCS-Activities of Daily Living Inventory – Severe Impairment Version (ADCS-ADL SIV) Score
Study design	This is a multicenter, prospective, phase IV study evaluating safety, tolerability and effectiveness of rivastigmine 27 mg -15 cm^2 transdermal patch prescribed in patients with severe dementia of the Alzheimer's type as per discretion of treating physician. The prescription decision shall be independent of decision for inclusion in the study. Patients treated according to local routine clinical practice will be enrolled in the study upon signing an Informed Consent. Eligibility for study entry will be determined by the study investigator, in accordance with the selection criteria below. Signing of the Informed Consent defines the study entry visit. Routine urine examination shall be done to detect any UTI. Compliance to treatment directions shall be reviewed by treating investigator at every visit. After 8 week and at 16 week, it is expected for the physician to follow up as per routine practice in India. The treating physician will assess the safety, tolerability and effectiveness of the rivastigmine 27 mg -15 cm2 transdermal patch and may consider continuing or changing the therapy
Population	Alzheimer's disease patients
Inclusion criteria	1. Patients willing to participate in the study by providing written informed consent. 2. Patients diagnosed with severe dementia secondary to Alzheimer's disease (AD)
Exclusion criteria	1. Contraindication as per PI 2. Patients simultaneously participating in other studies

Investigational and reference therapy	Rivastigmine patch 15cm2
Efficacy assessments	• Mini-Mental State Examination (MMSE) • ADCS-Activities of Daily Living Inventory – Severe Impairment Version (ADCS-ADL SIV) Score
Safety assessments	• Urine examination • Skin reaction at patch • Patch adhesion • Adverse events
Other assessments	• Compliance by Caregiver medication questionnaire
Data analysis	The primary safety objective of this study will be assessed by collecting adverse events. The key secondary objective of this study will be assessed by compliance measured by caregiver questionnaire, skin reaction and change in MMSE from baseline
Key words	Alzheimer, Rivastigmine,

1 Introduction

1.1 Background

1.2 Purpose

Alzheimer's disease (AD), a progressive neurodegenerative disorder, is the most prominent cognitive disorder of the elderly. The prevalence of AD in people over the age of 65 is 5-10%, and increases up to 50% in those over the age of 85 (Small GW, 1995). The Alzheimer's Association estimates that in 2008, as many as 5.2 million Americans have AD (Alzheimer's Association, 2008).

Multiple deficits of neurotransmitters occur in the brain of AD patients. However, the most common is a decrease in levels of acetylcholine (ACh), which is due to a loss of presynaptic cholinergic nerve terminals. These cholinergic deficits are most apparent in the areas of the brain involved in memory and cognition, i.e., the frontal cortex and hippocampus (Perry et al, 1978).

Currently, there are two compounds approved in the US for the treatment of severe dementia of the Alzheimer's type, the cholinesterase inhibitor donepezil and the glutamate modifying agent memantine. Both are often used together. With only one agent in each class available to treat patients with severe dementia of the Alzheimer's type, there is significant medical need to have other approved agents available, including those that have an alternative route to oral administration.

A number of treatment strategies involving the cholinergic system have been evaluated. Cholinesterase inhibitors (ChEIs), including rivastigmine (also known as ENA713 and Exelon®), have been shown to be effective in improving cognitive and global functioning in mild to moderate AD patients (Kumar et al, 1991; Knapp et al, 1994; Rogers et al, 1998; Corey-Bloom et al, 1998; Rösler et al, 1999; Raskind et al, 2000; Tariot et al, 2000).

Memantine has established efficacy in moderate to severe dementia of the Alzheimer's type (Reisberg et al, 2003; Tariot et al, 2004; van Dyck et al, 2007) and can be used as an augmenting agent with ChEIs.

The need for effective and well-tolerated treatments for AD (both symptomatic and disease modifying) remains great. Exelon® transdermal patch, prescribed once-daily, has the potential to offer improved caregiver and patient convenience in severe dementia of the Alzheimer's type, which may contribute to an improvement in patient compliance. In addition, this formulation is useful for patients unable to take oral medication. Exelon® (rivastigmine) is a slowly reversible (pseudo-irreversible), brain selective, dual inhibitor of Acetyl cholinesterase (AChE) and Butyryl cholinesterase inhibitors (BuChE) 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 present study is mandated by Indian health authority (HA) as a part of conditional approval to market authorization of rivastigmine 27 mg- 15 cm^2 transdermal patch for treatment of severe dementia secondary to Alzheimer's disease (AD).

Thus the present 16 week study will be conducted to evaluate safety, tolerability and effectiveness in patients with severe dementia of the Alzheimer's type exposed to rivastigmine 27 mg -15 cm2 transdermal patch as mandated by HA. Most frequent AEs in ACTION study were application site erythema/ dermatitis and UTI, the present study shall assess application site reaction and urine examination

2 Study objectives

2.1 Primary

Primary objective: To obtain safety data in patients with severe dementia of the Alzheimer's type treated with rivastigmine 27 mg -15 cm2 transdermal patch for 16 weeks

2.2 Secondary objectives

Secondary objectives:

- To assess patients compliance of rivastigmine 27 mg -15 cm2 transdermal patch during 16 weeks treatment period
- To assess the skin tolerability (irritation and adhesion) during 16 weeks treatment period
- To assess the proportion of patients with UTI during 16 weeks treatment period
- To evaluate treatment effect by rivastigmine 27 mg -15 cm2 transdermal patch by assessing the changes in Mini-Mental State Examination (MMSE)
- To evaluate treatment efficacy by rivastigmine 27 mg -15 cm2 transdermal patch by assessing the changes in ADCS-Activities of Daily Living Inventory – Severe Impairment Version (ADCS-ADL SIV) Score

2.3 Exploratory objectives

None

3 Investigational plan

3.1 Study design

This is a multicenter, prospective, phase IV study evaluating safety, tolerability and effectiveness of rivastigmine 27 mg -15 cm^2 transdermal patch prescribed in patients with severe dementia of the Alzheimer's type as per discretion of treating physician.

The prescription decision shall be independent of decision for inclusion in the study. Patients treated according to local routine clinical practice will be enrolled in the study upon signing an Informed Consent. Eligibility for study entry will be determined by the study investigator, in accordance with the selection criteria below. Signing of the Informed Consent defines the

study entry visit. Routine urine examination shall be done to detect any UTI. Compliance to treatment directions shall be reviewed by treating investigator at every visit.

After 8 week and at 16 week, it is expected for the physician to follow up as per routine practice in India. The treating physician will assess the safety, tolerability and effectiveness of the rivastigmine 27 mg -15 cm^2 transdermal patch and may consider continuing or changing the therapy.

3.2 Rationale of study design.

This is open label study to examine the safety, effectiveness, and tolerability of the treatment in routine clinical practice, to determine how the treatment works under ordinary and variable conditions, prescribed by clinicians with varying degrees of expertise and practicing across the spectrum of health care settings, to treat a heterogeneous group of patients.

3.3 Rationale of dose/regimen, route of administration and duration of treatment.

Dose and regimen is as per approved label in India for rivastigmine.

3.4 Rationale for choice of comparator

No comparator is used in study

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable

3.6 Risks and benefits

Rivastigmine is approved for the treatment of mild to moderately severe dementia of the Alzheimer type (and in some countries mild to moderately severe dementia associated with PD and severe dementia of the Alzheimer's type). In most cases the drug is used as a monotherapy, although in some cases it is used along with memantine. Prescription of the medication is initiated at a low dose and increased according to the patient's response and tolerance. Total period prescription numbers of the oral formulations are steadily decreasing to be replaced by increasing numbers of prescriptions of the transdermal (Patch) formulations. The treatment is initiated at patch 5cm2 and increased to patch 10 cm^2 after a minimum of four weeks of treatment if well tolerated and then, if appropriate to patch 15 cm2.

The benefit of rivastigmine has been seen in multiple clinical trials, in both placebo and active-controlled trials (using low dose Exelon as the active comparator). The ability of rivastigmine to positively affect the symptoms of AD and Parkinson's disease dementia has been demonstrated in six randomized double-blind, placebo-controlled clinical trials with 4517 patients with mild to moderate AD and in one randomized double blind placebo controlled trial with Parkinson's disease dementia with 541 patients. There was one (ENA713D2340) active controlled trial in mild to moderate AD with 1582 patients. There was one active controlled trial (US44 and US44E1) with extension for severe AD.

Clinically significant improvement in AD and Parkinson's disease dementia symptoms were observed in all but one clinical trial with response rates, in the transdermal formulations, achieved predominantly in patch 10 cm² and patch 15 cm2 users. Dementia improvement was seen in all tested demographics. The most frequently reported AEs were nausea, vomiting and diarrhea. This is consistent with Exelon's cholinergic effects and with results seen with Exelon® capsule. Action study with 15 cem Patch has demonstrated The 13.3 mg/24 h patch demonstrated superior efficacy to 4.6 mg/24 h patch on Severe Impairment Battery (SIB) and AD Cooperative Study–Activities of Daily Living scale–Severe Impairment Version (ADCS-ADL-SIV), without marked increase in AEs, suggesting higher-dose patch has a favorable benefit-to-risk profile in severe AD.

No pivotal clinical trials are ongoing except for CENA713D2409 which is a PASS drug utilization study to assess medication errors and misuse and multiple patch use in particular. All identified and potential risk are discussed in the Exelon RMP (version 8.0) and PSUR 24 (DLP 31 Jan 2016) and no new risks have been added and several have been removed in the last 2 PSURs. The sole risk with an ongoing risk minimization strategy is for medication errors(specifically multiple patch use) which is currently being actively implemented . Previous clinical trial results have been data-mined as a means for expanding MAH knowledge of the previously unstudied population of patients with pre-existing renal compromise and pre-existing cardiac disorders. No risk for use of rivastigmine in these populations has been detected to date. The company is continuing to investigate the increased reporting rate of skin reactions in the Japanese population which may result from intensive local pharmacovigilance collection techniques and determine if further measures are necessary.

The risk benefit ratio for Exelon (oral and transdermal formulations) remains positive.

4 Population

The study population will consist of male and female patients diagnosed with Alzheimer's disease and prescribed with rivastigmine 27mg -15 cm2 transdermal patch as per discretion of treating physician. Inclusion and exclusion criteria follow the approved indication and contraindications, as mentioned in package insert (PI) in India

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

- Patients willing to participate in the study by providing written informed consent.
- Patients diagnosed with severe dementia secondary to Alzheimer's disease (AD)
- Patient's prescribed with rivastigmine 27mg -15 cm2 transdermal patch as per discretion of treating physician

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

Exclusion criteria:

1. Contraindication as per PI

2. Patients simultaneously participating in other studies

4.3 Protocol requested treatment

4.3.1 Investigational treatment

The study will include the following open-label drug:
Exelon© patch: 15 cm2 patch sizes loaded with 27 mg of rivastigmine

4.3.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

4.4 Treatment arms.

Single arm study

4.5 Treatment assignment, randomization.

No protocol specific treatment will be assigned to subjects.

4.6 Treating the patient

4.6.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The reason for not being treated will be entered on the Screening Epoch Study Disposition CRF.

4.6.2 Dispensing the investigational treatment

Commercial Novartis drugs will be locally purchased.

4.6.3 Handling of study treatment.

Not applicable.

4.6.4 Handling of investigational treatment

Not applicable.

4.6.5 Instructions for prescribing and taking study treatment

The investigator should promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Refer to appendix 2 for instruction for applying the patch

4.6.6 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions are permitted in order to keep the patient on study drug. If necessary, the patient may be instructed to skip certain doses for a prescribed length of time (e.g., skip one or two day's doses) until tolerability has improved. The following treatment adjustment scheme is recommended:

- If tolerability problem arises: The caregiver should remove the patch(es) on the day the tolerability problems arise and skip 1 or 2 days of treatment.
- Tolerability should be reassessed after the patient has skipped the recommended days of treatment.
- If tolerability problems have improved, and consecutive days of missed doses is ≤ 3 days, treatment may be restarted at the same DL.
- If tolerability is still an issue, restart treatment at the next lower DL.
- The patient should then resume the titration schedule if tolerability issues have improved.
- If subsequent titration again leads to a tolerability problem, doses may again be skipped and the DL should be decreased to the next lower DL
- Further attempts to titrate the dose upward are at the investigator's discretion (i.e., if necessary for tolerability, titration to the target dose need not be achieved)

4.6.7 Rescue medication

Not applicable

4.6.8 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded.

4.6.9 Prohibited Treatment

No prohibited medication

4.6.10 Discontinuation of study treatment and premature patient withdrawal

The planned duration of the study is 16 weeks (+/- 2 weeks) and patients should be followed until the end of the study except if any of the following conditions for early termination are met:

- Voluntary discontinuation (withdrawal of consent to collect or use their data)

- Treatment discontinuation (patient no longer take the medication under observation)
- Addition of second AD treatment (patient no longer on monotherapy)

All data generated up to the time of voluntary discontinuation (withdrawal of consent) and the reason(s) for discontinuation will be recorded. Patients who choose to withdraw consent will no longer be contacted for follow up information.

Patients who discontinue treatment or patients who are no longer on monotherapy should be asked to return for an early discontinuation assessment. For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the physician should show "due diligence" by contacting the patients and asking them to return for a final assessment. Every effort should be made to obtain reason for discontinuation. The physician should document in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

4.6.11 Emergency breaking of treatment assignment

Not applicable

4.6.12 Study completion and post-study treatment

Study completion for an individual patient will be 16 weeks. At the end of study, patient would continue to receive treatment as per the discretion of Investigator.

4.6.13 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient’s interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Visit schedule and assessments

Error! Reference source not found. lists all of the assessments and indicates with an “x” when the visits are performed.

Examination	Baseline Visit 1 (Day 1)	Visit-2 (8 ± 2 weeks)	EOS Visit 3 (16 ± 2 weeks)
Informed consent	X		
Patient demographics (sex, age, etc)	X		
Relevant medical history	X		
Vitals	X	X	X
Physical examination*	X	X	X
Height** and weight	X	X	X
Inclusion/Exclusion criteria	X		
MMSE score	X	X	X
ADCS-ADL SIV score	X		X
Concomitant medications		X	X
Treatment for AD	X	X	X
Urine examination	X	X	X
Skin irritation assessment		X	X
Patch adhesion assessment		X	X
Adverse Events (AEs)and Serious Adverse Events (SAEs) recording	X	X	X
Compliance assessment using caregiver questionnaire		X	X
EOS			X

EOS = End of Study

X = Assessment to be recorded on CRF

**Physical examination includes examination of general appearance, skin, neck (including thyroid), eyes (excluding fundus), ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities. In addition, a neurological exam consisting of cranial nerve, motor and sensory assessments as performed in routine clinical practice. It also includes recording of pulse and blood pressure as per routine clinical care.*

*** Height is assessed only at Visit 1*

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit or following the last administration of study treatment), including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

5.1 Information to be collected on screening failures

For all patients who have signed informed consent and are entered into the next epoch of the study will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event CRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

5.2 Patient demographics/other baseline characteristics

- Date of birth or age and gender
- Relevant Medical history

At subsequent visits throughout the observation period, the following information will be updated:

- Change in concomitant medications
- Treatment taken for AD
- Physical examination which includes examination of general appearance, skin, neck (including thyroid), eyes (excluding fundus), ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities. In addition, a neurological exam consisting of cranial nerve, motor and sensory assessments as performed in routine clinical practice.It also includes recording of pulse and blood pressure as per routine clinical care
- Mini-Mental State Examination (MMSE)
- ADCS-ADL SIV score

5.3 Treatment exposure and compliance

Study drug patch administered during the course of the study will be recorded on the corresponding Dosage Administration Record CRF
Other drugs administered prior to and continuing at start of study medication will be entered on the 'Concomitant medications/significant non-drug therapies prior to the start of study' CRF.

Compliance will be assessed by the investigator and/or study personnel at each visit using information provided by the patient. This information should be captured in the source document at each visit

5.4 Efficacy

5.4.1 Efficacy assessment

Mini-Mental State Examination (MMSE):

Assessing the changes in Mini-Mental State Examination (MMSE): The MMSE is a brief, practical screening test for cognitive dysfunction (Folstein et al. 1975). The test consists of

five sections (orientation, registration, attention-calculation, recall, and language & Praxis) and results in a total possible score of 30, with higher scores indicating better function. MMSE shall be recorded at the start and at each visit as mentioned in table 5.1as a part of routine clinical practice.

ADCS-ADL SIV score*:

This is a tool to assess the ability of patients with moderate to severe dementia to perform activities of daily living. ADCS-ADL SIV score is done at start and end of visit. This includes 19 questions and total score is 54. Administration instructions and Instruction card for the rater to use when administering the scale is separately provided

*"Used with permission from the NIA Alzheimer's Disease Cooperative Study (NIA Grant AG10483)".

5.4.2 Appropriateness of efficacy assessments

MMSE and ADCS-ADL SIV score is standard assessment tool for cognitive examination

5.5 Safety

5.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing the informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.

5.5.2 Dermatology examination:

The following score system will be used to assess skin irritation:

I. Dermal response:

0 = No erythema (normal skin)

1 = Erythema barely visible

2 = Mild erythema

3 = Moderate erythema

4 = Severe erythema

5 = Severe erythema with vesicles or blisters

II. Other effects:

O : Edema

P : Papules (many small, red, solid, elevated lesions, surface of reaction with granular feeling)

V : Small vesicles (< 0.5 cm) circumscribed elevations with visible fluid

B : Large blister (> 0.5 cm) circumscribed elevations with visible fluid

Pu : Pustules (inflammatory small elevations containing purulent exudate)

H : Hyperpigmentation (increase of the usual pigmentation limited to the patch test area)

W : Weeping or oozing (may be a sign of vesiculation or blistering manifested by crusting)

S : Extension of the reaction beyond patch-test site (on skin area where no test product was applied)

A : Marked reaction to adhesive patch

5.5.3 Vital signs

5.5.4 Vital signs include Body temperature, BP and pulse and respiratory rate measurements. Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

5.5.5 Patch adhesion assessment:

For the patients randomized to the Exelon® patch treatment, patch adhesion to the skin will be evaluated by the caregiver. An estimate of the patch adherence will be provided and graded according to the patch adhesiveness score for the intervals between the scheduled outpatient visits.

Following scores should be used to capture comments relating to patch adhesion:

0 = 90 % adhered (essentially no lift off of the skin)

1 = 75% to < 90% adhered (some edges only lifting off of the skin)

2 = 50% to < 75% adhered (less than half of the patch lifting off the skin)

3 = < 50% adhered but not detached (more than half the system lifting off of the skin without falling off)

4 = the patch was completely detached

5.5.6 Laboratory evaluations

5.5.6.1 Urinalysis

Complete urine examination will be done at baseline, visit 2 and end of study visit.

5.5.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

5.6 Other assessments

5.6.1 Treatment and compliance:

Caregiver medication questionnaire: Caregiver evaluation of the medications used for AD will be assessed using the Caregiver Medication Questionnaire (CMQ). The CMQ contains 4 items, which focus on caregiver evaluation of medication administration and following schedule, and 2 global items asking about caregiver perceived compliance and satisfaction..

The CMQ questionnaire asks the caregiver to respond to the items based on the patch that the patient was taking during this study.

5.6.2 Health-related Quality of Life

Not done

5.6.3 Pharmacokinetics

Not done

5.6.4 Pharmacogenetics/pharmacogenomics

Not done

5.6.5 Other biomarkers:

Not done

6 Safety monitoring

6.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them accompanied by the following information.

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment (no/yes), or
  its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding study treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

An SAE is any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); [study treatment/investigational] treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the package insert. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

6.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days [after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures] must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (*either initial or follow up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship to drug, complete the SAE Report Form in English, and send the completed, signed form by email/fax within 24 hours after awareness of the SAE to the local Novartis Patient Safety Department. The contact details of local Patient Safety are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and acknowledgement must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Package Insert (new occurrence) and is thought to be related to the investigational treatment, a Novartis Patient Safety Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue Biannual Suspected Unexpected Serious Adverse Reaction (SUSAR) Line listing to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. All SAE will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

6.3 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Patient Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7 Data review and database management

7.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator’s meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study. treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. *[Data not requiring a separate written record will be defined before study start*

and will be recorded directly on the CRFs.] The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

7.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the Novartis CRFs that are printed on X *[specify number of copies – i.e. 3-part]*-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to the Medical Documents Reception Center of Novartis *[or CRO working on behalf of Novartis]* by field monitors or by the investigational site, with one copy being retained at the investigational site. Once the CRFs are received by Novartis *[or CRO working on behalf of Novartis]*, their receipt is recorded, the original copy is placed in Central Files, and the non-carbon-required copy is forwarded to the responsible Data Management staff for processing

7.3 Data Monitoring Committee

Not required.

7.4 Adjudication Committee

Not required.

8 Data analysis

All analyses will be performed by Novartis or a designated CRO.

Descriptive analyses will include n, mean, standard deviation, median, first quartile, third quartile and ranges for continuous variables and frequencies and percentages for categorical variables. Summaries will be presented together with estimates and corresponding 95% confidence intervals (CI) as appropriate

8.1 Analysis sets

The **intend to treat (IIT) set** will include all patients having signed the Informed Consent, who have at least one post baseline assessment.

The **safety set** will include all patients who provide Informed Consent to collect information and who were treated with at least one patch of rivastigmine 27 mg- 15 cm^2 transdermal patch during this study,. Of note, the statement that a patient had no AE also constitutes a safety assessment.

All analyses will be carried out on the ITT set, while adverse event analyses will be conducted in the safety set.

All patient demographics, medical history, prior treatments, and other baseline characteristics will be presented using standard descriptive statistics. Use of concomitant medication will be summarized using frequency counts and percentages by treatment group for patients in the Safety Set

8.2 Patient demographics and other baseline characteristics

All patient demographics, medical history, prior treatments, and other baseline characteristics will be presented using standard descriptive statistics

8.3 Treatments

Use of concomitant medication will be summarized using frequency counts and percentages by treatment group for patients in the Safety Set.

8.4 Analysis of the primary and key secondary variable(s)

8.4.1 Primary Variable

8.4.2 Statistical model, hypothesis, and method of analysis

The primary variable analysis will be performed on the safety set. No hypothesis is built for the study

8.4.3 Handling of missing values/censoring/discontinuations.

LOCF (last observation carried forward) method will be used for missing values at week 16

8.4.4 Supportive analyses

Not planned

8.5 Analysis of secondary variables

8.5.1 Efficacy variables

The change from baseline in MMSE total score of 11 items will be summarized for the study. For Responses on the Caregiver Medication Questionnaire Mean scores will be computed for each of the other items in CMQ

Change in the ADCS-Activities of Daily Living Inventory – Severe Impairment Version (ADCS-ADL SIV) Score will be summarized for the study

8.5.2 Safety variables

All safety analyses will be performed on the Safety Set. Adverse events (AEs) will be coded utilizing the MedDRA dictionary. AEs will be summarized by presenting the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. For the safety analysis, all treatment emergent adverse events will be summarized and listed. The following treatment emergent adverse event summaries will be produced: overall by system organ class and preferred term, overall by system organ class, preferred term and maximum severity, suspected drug-related adverse events by system organ class and preferred term, serious adverse event by system organ class and preferred term, and adverse events leading to permanent discontinuation of study-medication by system organ class and preferred term. Any other information collected (e.g. severity or relatedness to study medication) will also be summarized as appropriate. For each skin irritation scale, summary statistics will be provided by time and treatment group. When appropriate, two-sided 95%-confidence intervals for means and/or proportions as well as p-values will be provided. The p-values will be used in a non-confirmatory manner.

Further details will be outlined in the SAP

8.5.3 Resource utilization

NA

8.5.4 Health-related Quality of Life

8.5.5 Pharmacokinetics

8.5.6 Pharmacogenetics/pharmacogenomics

NA

8.5.7 Biomarkers

NA

8.5.8 PK/PD

NA

8.6 Interim analyses

No interim analyses planned

8.7 Sample size calculation

Incidence of adverse event data of ACTION study (74.60%) for Rivastigmine patch per day over a 24-week study period in patients with severe AD.

Sample size is determined based on a precession approach considering normal approximation. A sample of 93 subjects will be able to estimate the incidence rate with an maximum error of

10% of the true population proportion with 90% of the cases. We assumed, the true population proportion is 0.746 (what is observed in US44)

Similarly, a sample of 41 subjects will be able to estimate the incidence rate with an maximum error of 10% of the true population proportion with 85% of the cases and sample of 23 subjects of the true population proportion with 80% of the cases.

Considering drop out of 10% and true population proportion with 90%, 102 patients shall be enrolled.

9 Ethical considerations

9.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

9.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

9.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and

informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

9.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

10.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

11 References:

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14. Farlow M, Grossberg G, Sadowsky CH, Meng X, Somogyi M. (2013) A 24-Week, Randomized, Controlled Trial of Rivastigmine Patch 13.3 mg/24 h Versus 4.6 mg/24 h in Severe Alzheimer's Dementia. CNS Neuroscience & Therapeutics, 19(10): 745–752

12 Appendix 1– Caregiver Medication Questionnaire

For each part of every question, please choose only one answer per row. Please mark your answers by placing an 'X' in the box or circling a number.

Please answer all of the questions as honestly as you can and without help from anyone. There are no wrong answers.

All of the information you provide will be kept confidential

For the following questions, please respond based on the patch medication for Alzheimer's disease that the person for whom you provide care has been taking during this study.

1. During the **past 1 week**, to the best of your knowledge, how often was...

(Check ☑ one answer for each question below)

	NEVER	1 DAY	2 DAYS	3 DAYS	4 OR MORE DAYS
a. a patch ever skipped?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. the patch taken later than intended	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Taking your medication in the dose and at the times prescribed can be very important to the action of the medication. During the **past 1 week of therapy with the patch medication for Alzheimer's disease**, to the best of your knowledge:

2. To what extent would you agree with the following :

(Check ☑ one answer for each question below)

	ALWAYS	MOST OF THE TIME	SOMETIMES	RARELY	NEVER
a. I was concerned that my patient missed taking his/her patch medication	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I found it difficult to remember to administer the patch medication	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. Please think about compliance with the patch, which means taking the patch as it is prescribed on a daily basis. Please rate the overall compliance with taking the medication on a scale from 0 to 10.

0 1 2 3 4 5 6 7 8 9 10

NEVER TOOK THE MEDICATION AS PRESCRIBED — *(Circle one number above)* — ALWAYS TOOK THE MEDICATION AS PRESCRIBED

4. Taking all things into account, how satisfied or dissatisfied are you with the patch?

0 1 2 3 4 5 6 7 8 9 10

EXTREMELY DISSATISFIED — *(Circle one number above)* — EXTREMELY SATISFIED

13 Appendix 2: Patient Instructions for use and handling exelon patch

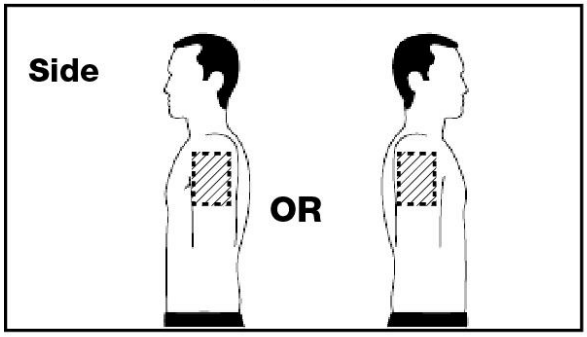
Only one patch should be worn at a time. Remove the previous day's Exelon Patch before applying a new one. Do not cut the patch into pieces.

Where to apply Exelon Patch

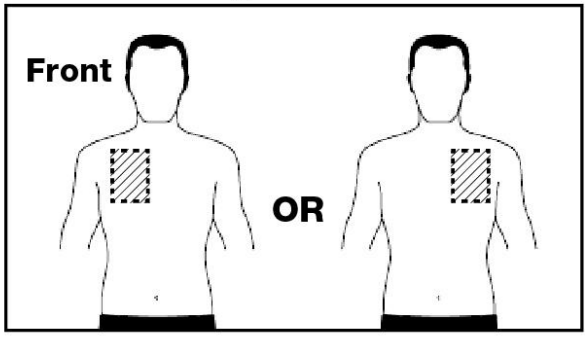
- Before you apply Exelon Patch, make sure that your skin is:
  - clean, dry and hairless
  - free of any powder, oil, moisturiser, or lotion (that could keep the patch from sticking to your skin properly)
  - free of cuts, rashes and/or irritations.
- **Every 24 hours, please gently remove any existing Exelon patch before putting on a new one. Having multiple patches on your body could expose you to an excessive amount of this medicine which could be potentially dangerous.**
- Apply **ONLY ONE** patch per day to **ONLY ONE** of the following locations (shown in the figures below):
  - upper arm, left **or** right side, **or**
  - chest, left **or** right side, **or**
  - upper back, left **or** right side, **or**
  - lower back, left **or** right side,

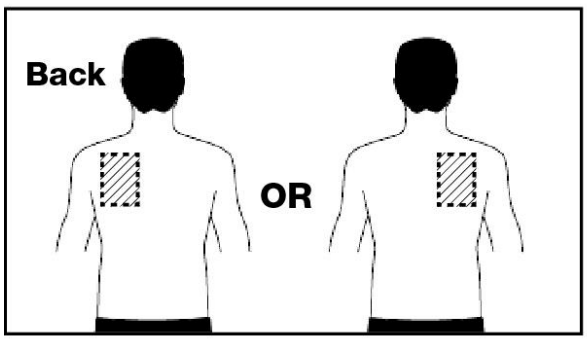
Avoid places where the patch can be rubbed off by tight clothing.

Left or Right Upper Arm

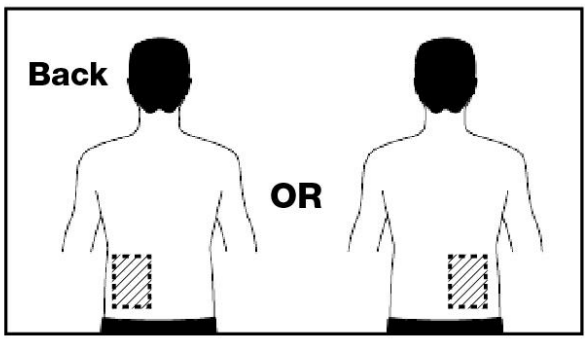


Left or Right Side of Chest





Left or Right Upper Back



Left or Right Lower Back

When changing your patch, you must remove the previous day's patch before you apply your new patch to a different area of skin (for example on the right side of your body one day, then on the left side the next day). Do not apply a new patch to that same area for at least one week.

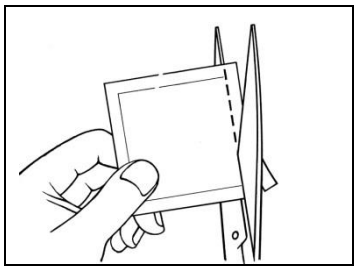
How to apply Exelon Patch

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

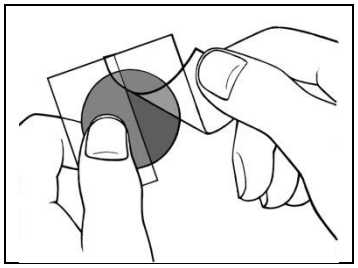
Every 24 hours, please gently remove any existing Exelon patch before putting on a new one. Having multiple patches on your body could expose you to an excessive amount of this medicine which could be potentially dangerous.

- Each patch is sealed in its own protective sachet.
  You should only open the sachet when you are ready to apply the patch.

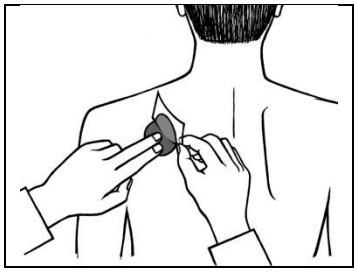
  Tear or cut the sachet at the notch and remove the patch.



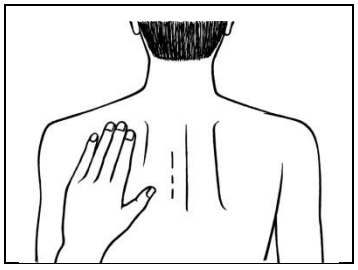
- A protective liner covers the adhesive side of the patch.
  Peel off one side of the protective liner and do not touch the sticky part of the patch with the fingers.



- Put the sticky side of the patch on the upper or lower back, upper arm or chest and then peel off the second side of the protective liner.



- Then press the patch firmly in place **for at least 30 seconds** using the palm of the hand to make sure that the edges stick well.

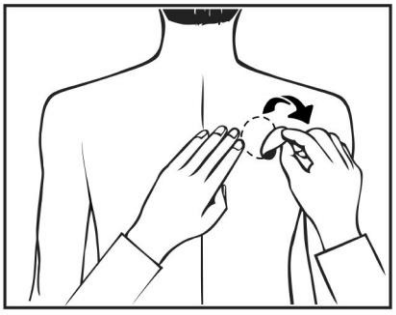


- If it helps you, you may write (e.g. the day of the week) on the Exelon Patch with a thin ball point pen.

Exelon Patch should be worn continuously until it is time to replace it with a new patch. You may wish to experiment with different locations when applying a new patch, to find ones that are most comfortable for you and where clothing will not rub on the patch.

How to remove Exelon Patch

Gently pull at one edge of the Exelon Patch to remove it completely from the skin.



In case the adhesive residue is left over on your skin, gently soak the area with warm water and mild soap or use baby oil to remove it. Alcohol or other dissolving liquids (nail polish remover or other solvents) should not be used.

How to dispose Exelon Patch

After the patch has been removed, fold it in half with the adhesive sides on the inside and press them together. Return the used patch to its original sachet and discard safely out of the reach and sight of children. Wash your hands with soap and water after removing the patch. In case of contact with eyes or if the eyes become red after handling the patch, rinse immediately with plenty of water and seek medical advice if symptoms do not resolve.

Can you wear the patch when bathing, swimming, or in the sun?

- Bathing, swimming, or showering should not affect the patch. When swimming, you can wear the patch under your swimming costume. Make sure the patch does not loosen during these activities.
- The patch should not be exposed to any external heat sources (excessive sunlight, saunas, solarium) for long periods of time.

What to do if Exelon Patch falls off

If the patch falls off, a new patch should be applied for the rest of the day, then replace the patch the next day at the same time as usual.