NOVARTIS

Exelon® Patch

Brain-selective cholinesterase inhibitor

DESCRIPTION AND COMPOSITION

Pharmaceutical form

Transdermal patch.

Each transdermal patch is a thin, matrix-type transdermal patch consisting of three layers.

The outside of the backing layer is beige and labelled for each patch as follows:

- for Exelon Patch 5; "AMCX"
- for Exelon Patch 10; "BHDI"
- for Exelon Patch 15; "CNFU".

Active substance

Each Exelon Patch 5 transdermal patch releases 4.6mg of rivastigmine per 24 hours. Each transdermal patch of 5 cm^2 contains 9 mg rivastigmine.

Each Exelon Patch 10 transdermal patch releases 9.5mg of rivastigmine per 24 hours. Each transdermal patch of 10 cm^2 contains 18 mg rivastigmine.

Each Exelon Patch 15 transdermal patch releases 13.3mg of rivastigmine per 24 hours. Each transdermal patch of 15 cm^2 contains 27 mg rivastigmine.

Excipients

Backing layer: polyethylene terephthalate film, lacquered

Medicinal product matrix: alpha-tocopherol, poly (butylmethacrylate, methyl-methacrylate), acrylic copolymer

Adhesive matrix: alpha tocopherol, silicone oil, dimethicone

Release liner: polyester film, fluoropolymer-coated

INDICATIONS

Patch 5, 10 & 15

Symptomatic treatment of mild to moderately severe, and severe Alzheimer's dementia.

Patch 5 & 10

Symptomatic treatment of mild to moderate dementia associated with Parkinson's disease. It is generally recommended to those patients in whom the administration of oral Exelon capsules is unsuitable or infeasible.

DOSAGE REGIMEN AND ADMINISTRATION

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Diagnosis should be made according to current guidelines. Similar to any treatment initiated in patients with dementia, therapy with rivastigmine should only be started if a caregiver is available to regularly administer and monitor the treatment.

Posology

Patches	Rivastigmine base dose load	Rivastigmine base *in vivo* release rates per 24 h
Exelon Patch 5 (4.6mg/24 h)	9 mg	4.6 mg
Exelon Patch 10 (9.5mg/24 h)	18 mg	9.5 mg
Exelon Patch 15 (13.3mg/24hr)	27 mg	13.3 mg

Mild to moderately severe Alzheimer's dementia

Initial dose and dose titration to the effective dose:

Treatment is started with 4.6mg/24 h.

After a minimum of four weeks of treatment and if well tolerated according to the treating physician, this dose should be increased to 9.5mg/24 h, the recommended effective dose, which can be continued for as long as the patient is deriving therapeutic benefit.

If well tolerated and only after a minimum of six months of treatment at 9.5 mg/24 h, the treating physician may consider increasing the dose to 13.3 mg/24 h in patients who have demonstrated a meaningful cognitive deterioration (e.g., decrease in the MMSE) and/or functional decline (based on physician judgement) while on the recommended daily effective dose of 9.5 mg/24h (see section CLINICAL STUDIES).

Severe dementia of the Alzheimer's type

Initial dose and dose titration to the effective dose: Treatment is started with 4.6mg/24h once a day. Subsequently the dose should be increased to 9.5mg/24h and then to 13.3mg/24hr which is the demonstrated effective dose. These dose increases should always be based on good tolerability of the current dose and may be considered only after a minimum of four weeks of treatment at each dose level.

Interruption of treatment

Treatment should be temporarily interrupted if gastrointestinal adverse effects are observed until these adverse effects resolve. Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than several days. Otherwise, treatment should be re-initiated with 4.6mg/24 h.

Switching from capsules or oral solution to transdermal patches

Based on comparable exposure between oral and transdermal rivastigmine (see Pharmacokinetics), patients treated with Exelon capsules or oral solution can be switched to Exelon patches as follows:

- A patient on a dose of 3 mg/day oral rivastigmine can be switched to 4.6mg/24 h transdermal patches.
- A patient on a dose of 6 mg/day oral rivastigmine can be switched to 4.6mg/24 h transdermal patches.
- A patient on a stable and well tolerated dose of 9 mg/day oral rivastigmine can be switched to 9.5 mg/24 h transdermal patches. If the oral dose of 9mg/day has not been stable and well tolerated, a switch to 4.6 mg/24 h transdermal patches is recommended.
- A patient on a dose of 12 mg/day oral rivastigmine can be switched to 9.5mg/24 h transdermal patches.

After switching to 4.6mg/24 h transdermal patches, provided these are well tolerated after a minimum of four weeks of treatment, the dose of 4.6 mg/24 h should be increased to 9.5mg/24 h, which is the recommended effective dose.

It is recommended to apply the first transdermal patch on the day following the last oral dose.

Method of administration

Transdermal patches should be applied once a day to clean, dry, hairless, intact healthy skin on the upper or lower back, upper arm, or chest, in a place which will not be rubbed by tight clothing. It is not recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine observed when the transdermal patch is applied to these areas of the body.

The transdermal patch should be replaced by a new one after 24 hours.

Important administration instructions (patients and caregivers should be instructed)

- The previous day's patch must be removed before applying a new one.
- The patch should be replaced by a new one after 24 hours. Only one patch should be worn at a time (see sections WARNINGS AND PRECAUTIONS and OVERDOSAGE).
- The patch should not be applied to skin that is red, irritated, or cut. Reapplication to the exact same skin location within 14 days should be avoided to minimize the potential risk of skin irritation.
- The transdermal patch should be pressed down firmly for at least 30 seconds using the palm of the hand until the edges stick well.
- If the patch falls off, a new one should be applied for the rest of the day, then it should be replaced at the same time as usual the next day.
- The patch can be used in everyday situations, including bathing and during hot weather.
- The patch should not be exposed to any external heat sources (e.g., excessive sunlight, saunas, solarium) for long periods of time.
- The patch should not be cut into pieces.
- Wash your hands with soap and water after applying/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.

Special populations

Patients with body weight below 50 kg

Caution should be exercised in titrating these patients as they may experience more adverse reactions. Carefully titrate and monitor these patients for adverse reactions (e.g., excessive nausea or vomiting) and consider reducing the dose if such adverse reactions develop (see section WARNINGS AND PRECAUTIONS).

Hepatic impairment

Due to increased exposure in mild to moderate hepatic impairment, as observed with the oral formulation, dosing recommendations to titrate according to individual tolerability should be closely followed. Patients with clinically significant hepatic impairment may experience more dose dependent adverse reactions. Patients with severe hepatic impairment have not been studied. Particular caution should be exercised in titrating these patients (see sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY – PHARMACOKINETICS).

Renal impairment

No dose adjustment is necessary for patients with renal impairment (see CLINICAL PHARMACOLOGY – Pharmacokinetics).

Paediatric patients (below 18 years)

The use of Exelon in paediatric patients has not been studied and is therefore not recommended.

CONTRAINDICATIONS

The use of Exelon is contraindicated in patients with:

- known hypersensitivity to rivastigmine, to other carbamate derivatives or to the excipients of the formulation (see section DESCRIPTION AND COMPOSITION - Excipients)
- previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine transdermal patch (see section WARNINGS AND PRECAUTIONS – Application site reactions and skin reactions)

WARNINGS AND PRECAUTIONS

Medication misuse and dosing errors resulting in overdose

Medication misuse and dosing errors with Exelon transdermal patch have resulted in serious adverse reactions; some cases have required hospitalization, and rarely led to death (see section OVERDOSAGE). The majority of medication misuse and dosing errors have involved not removing the old patch when putting on a new one and the use of multiple patches at one time. Patients and their caregivers must be instructed on important administration instructions for Exelon transdermal patch (see section DOSAGE REGIMEN AND ADMINISTRATION).

Gastrointestinal disorders

The incidence and severity of adverse events generally increase with increasing doses, particularly at dose changes. If treatment is interrupted for more than several days, it should be re-initiated with 4.6mg/24 h.

Gastrointestinal disorders such as nausea, vomiting and diarrhoea are dose related, and may occur when initiating treatment and/or increasing the dose. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhoea can be managed with iv fluids and dose reduction or discontinuation if recognized and treated promptly. Dehydration can be associated with serious outcomes (see ADVERSE DRUG REACTIONS).

Weight loss

Patients with Alzheimer's disease may lose weight while taking cholinesterase inhibitors, including rivastigmine. The patient's weight should be monitored during therapy with Exelon transdermal patches.

Other adverse reactions from increased cholinergic activity

As with other cholinergic substances, care must be taken when prescribing Exelon transdermal patches:

- to patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see ADVERSE DRUG REACTIONS).

- to patients with active gastric or duodenal ulcers or patients predisposed to these conditions because rivastigmine may cause increased gastric secretions (see ADVERSE DRUG REACTIONS).
- to patients predisposed to urinary obstruction and seizures because cholinomimetics may induce or exacerbate these diseases.
- to patients with a history of asthma or obstructive pulmonary disease.

As with other cholinergic substances, rivastigmine may induce or exacerbate or induce extrapyramidal symptoms. In patients with dementia associated with Parkinson's disease who were treated with Exelon capsules, worsening of parkinsonian symptoms, particularly tremor, has been observed. Such adverse events may also occur with Exelon patches, particularly with Exelon 13.3mg/24 h transdermal patch which provide higher exposure (AUC) than that achieved with twice-daily administration of Exelon 6 mg capsules.

Contact with the eyes should be avoided after handling Exelon transdermal patches (see NON-CLINICAL SAFETY DATA)

QT prolongation and torsade de pointes

Electrocardiogram QT prolongation may occur in patients treated with certain cholinesterase inhibitor products including rivastigmine. Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, hypokalaemia or hypomagnesemia, personal or family history of QT prolongation, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes. Clinical monitoring may also be required (see INTERACTIONS).

Application site reactions and skin reactions

Skin application site reactions may occur with Exelon Patch and are usually mild or moderate in intensity (see section ADVERSE DRUG REACTIONS – Application site reactions). These reactions are not in themselves an indication of sensitization. However, use of rivastigmine patch may lead to allergic contact dermatitis.

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g., increasing erythema, edema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see section CONTRAINDICATIONS).

In patients who develop application site reactions suggestive of allergic contact dermatitis to Exelon Patch and who still require rivastigmine, treatment should be switched to oral rivastigmine only after negative allergy testing and under close medical supervision. It is possible that some patients sensitized to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

There have been isolated post-marketing reports of patients experiencing allergic dermatitis (disseminated) when administered rivastigmine irrespective of the route of administration (oral, transdermal). In these cases, treatment should be discontinued (see section CONTRAINDICATIONS). Patients and caregivers should be instructed accordingly.

Special populations

- Patients with body weight below 50 kg may experience more adverse reactions and may be more likely to discontinue due to adverse reactions. Carefully titrate and monitor these patients for adverse reactions (e.g., excessive nausea or vomiting) and consider reducing the dose if such adverse reactions develop (see section DOSAGE REGIMEN AND ADMINISTRATION).
- Hepatic impairment: Patients with clinically significant hepatic impairment may experience more adverse reactions. Dosing recommendations to titrate according to individual tolerability should be closely followed. Patients with severe hepatic impairment have not been studied. (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY – Pharmacokinetics).

Driving and using machines

Alzheimer's disease may cause gradual impairment of driving performance or compromise the ability to use machinery. Furthermore, rivastigmine may induce syncope or delirium. Therefore, in patients with dementia treated with rivastigmine, the ability to continue driving or operating complex machines should be routinely evaluated by the treating physician.

ADVERSE DRUG REACTIONS

The overall incidence of adverse events (AEs) in patients treated with Exelon 9.5mg/24 h transdermal patches was lower than the rate in patients who received 3 to 12 mg/day Exelon capsule treatment (50.5% with Exelon 9.5mg/24 h transdermal patches vs 63.3% with Exelon capsules; 46.0% of patients on placebo reported AEs). Gastrointestinal adverse events, including nausea and vomiting, were the most common adverse events in patients who received active treatment, and occurred at a substantially lower rate in the Exelon 9.5mg/24 h transdermal patch group compared to the Exelon capsule group (7.2% vs 23.1% for nausea and 6.2% vs 17.0% for vomiting; 5.0% and 3.3% of patients on placebo reported nausea and vomiting, respectively).

Adverse drug reactions from clinical trials in Table 1 and Table 2 are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).

Table 1 Adverse drug reactions reported in 2,687 patients with Alzheimer's dementia treated for 24 weeks to 48 weeks in randomized controlled clinical studies with Exelon patches at all doses (Exelon Patch 5 to Exelon Patch 20)

Metabolism and nutrition disorders	
Common:	Anorexia, decreased appetite

Uncommon	Dehydration
Psychiatric disorders	
Common:	Anxiety, depression, insomnia
Uncommon:	Agitation, delirium, hallucinations, aggression
Nervous system disorders	
Common:	headache, dizziness
Uncommon:	Cerebrovascular accident, syncope, somnolence*, psychomotor hyperactivity
Cardiac disorders	
Uncommon:	Cardiac arrhythmia (e.g., Bradycardia, supraventricular extrasystole)
Gastrointestinal disorders	
Very common:	Nausea
Common:	Vomiting, diarrhoea, dyspepsia, abdominal pain
Uncommon:	Gastric ulcer, gastrointestinal haemorrhage (e.g., Haemorrhagic duodenitis)
Renal and urinary disorders	
Common	Urinary incontinence
Skin and subcutaneous tissue disorders	
Common:	Rash
Uncommon:	Hyperhidrosis
General disorders and administration site conditions	
Common:	Application site reactions, application site erythema, application site pruritus**, application site oedema**, fatigue, asthenia, pyrexia
Uncommon:	Contact dermatitis**, malaise
Rare	Fall
Investigations	
Common:	Weight decrease
Infections and infestations	
Common:	Urinary tract infection

*In a 24-week-controlled study in Chinese patients' somnolence was reported as "common".

**In a 24-week-controlled study in Japanese patients, application site erythema, application site oedema, application site pruritus and contact dermatitis were reported as "very common".

Table 2 Adverse drug reactions reported in 24-week period in the open-label clinical study conducted with Exelon transdermal patches in patients with dementia associated with Parkinson's disease.

Adverse drug reactions		**Exelon Patch n (%)**
Total patients studied		288 (100)
Psychiatric disorders		
Common:	Insomnia	18 (6.3)
Common:	Depression	16 (5.6)
Common:	Anxiety	15 (5.2)
Common:	Agitation	8 (2.8)

Nervous system disorders		
Common:	Tremor	21 (7.3)
Common:	Dizziness	16 (5.6)
Common:	Somnolence	12 (4.2)
Common:	Hypokinesia	11 (3.8)
Common:	Bradykinesia	10 (3.5)
Common:	Cogwheel rigidity	8 (2.8)
Common:	Dyskinesia	7 (2.4)
Gastrointestinal disorders		
Common:	Abdominal pain	6 (2.1)
Vascular disorders		
Common:	Hypertension	9 (3.1)
General disorders and administration site conditions		
Very Common:	Fall	34 (11.8)
Very Common:	Application site erythema	31 (10.8)
Common:	Application site irritation, pruritus, rash	9 (3.1); 13 (4.5);7 (2.4)
Common:	Fatigue	10 (3.5)
Common:	Asthenia	6 (2.1)
Common:	Gait disturbance	11 (3.8)

Additional adverse reactions observed during a 76-week prospective, open-label study in patients with dementia associated with Parkinson's disease treated with Exelon transdermal patches: dehydration, decreased weight, aggression, visual hallucination (common).

In patients with dementia associated with Parkinson's disease the following adverse drug reactions have only been observed in clinical trials with Exelon capsules: nausea, vomiting (very common); decreased appetite, restlessness, worsening of Parkinson's disease, bradycardia, diarrhoea, dyspepsia, salivary hypersecretion, increased sweating (common); dystonia, atrial fibrillation, atrioventricular block (uncommon).

Adverse drug reactions from post-marketing spontaneous reports

The following additional adverse drug reactions have been identified based on post-marketing spontaneous reports. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Rarely reported: hypertension, application site hypersensitivity, pruritus, erythema, urticaria, blister, dermatitis allergic.

Very rarely reported: tachycardia, atrioventricular block, atrial fibrillation, pancreatitis, fall, seizure. Parkinson's disease (worsening) has been observed in patients with Parkinson's disease who were treated with Exelon patches.

Frequency not known: hepatitis, restlessness, sick sinus syndrome, abnormal liver function tests, allergic dermatitis (disseminated), extrapyramidal symptoms in patients with Alzheimer's dementia, tremor, nightmares.

Additional adverse drug reactions which have been reported with Exelon capsules or oral solution

Very rare: severe vomiting associated with oesophageal rupture

Rare: angina pectoris, myocardial infarction, duodenal ulcers.

Common: confusion.

Information from clinical trials in patients with severe Alzheimer's dementia treated with Exelon Patch 15

The following adverse drug reactions were reported in patients with severe Alzheimer's dementia treated with Exelon Patch 15.

Table 3 Adverse drug reactions (≥5% in either Exelon Patch groups) from the 24-week double-blind randomized controlled clinical trial conducted with Exelon Patch 15 in patients with severe Alzheimer's dementia

Preferred term	Exelon Patch 15 group n (%)	Exelon Patch 5 group n (%)
Total patients studied	355	359
Total number of patients with AE(s)	265 (74.6)	263 (73.3)
Application site erythema	47 (13.2)	42 (11.7)
Agitation	41 (11.5)	51 (14.2)
Urinary tract infection	29 (8.2)	34 (9.5)
Fall	27 (7.6)	21 (5.8)
Insomnia	25 (7.0)	15 (4.2)
Vomiting	25 (7.0)	9 (2.5)
Diarrhoea	23 (6.5)	19 (5.3)
Weight decreased	23 (6.5)	11 (3.1)
Nausea	22 (6.2)	10 (2.8)
Depression	17 (4.8)	15 (4.2)
Decreased appetite	17 (4.8)	5 (1.4)
Anxiety	16 (4.5)	16 (4.5)
Hallucination	7 (2.0)	16 (4.5)

Application site reactions (skin irritation)

In double-blind controlled clinical trials, application site reactions were mostly mild to moderate in severity. The incidence of application site skin reactions leading to discontinuation was observed in ≤2.3% of Exelon Patch patients. This number was 4.9% and 8.4% in the Chinese population and Japanese population, respectively.

Cases of skin irritation were captured separately on an investigator-rated skin irritation scale. In this study, the most commonly observed symptoms (skin irritation rating scale) with Exelon 9.5mg/24 h transdermal patches were very slight (21.8%), mild (12.5%) or moderate (6.5%) erythema or very slight (11.9%), mild (7.3%) or moderate (5.0%) pruritus. The most commonly observed severe symptoms with Exelon 9.5mg/24 h transdermal patches were pruritus (1.7%) and erythema (1.1%). Most skin reactions were limited to the application site and resulted in discontinuation in only 2.4% of the patients in the Exelon 9.5mg/24 h transdermal patch group.

See section WARNINGS AND PRECAUTIONS – Application site reactions and skin reactions.

INTERACTIONS

No specific interaction studies have been conducted with Exelon transdermal patches.

Anticipated interactions resulting in a concomitant use not recommended

Metoclopramide

Considering the possibility of an additive extra-pyramidal effect the concomitant use of metoclopramide and rivastigmine is not recommended.

Drugs acting on cholinergic system

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic drugs due to possible additive effect. Rivastigmine might also interfere with the activity of anticholinergic medications (e.g., oxybutynin, tolterodine).

Succinylcholine-type muscle relaxants

As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia.

Anticipated interactions to be considered

Medicinal products known to prolong the QT interval

Caution is advised when rivastigmine is used in combination with other medicinal products known to prolong the QT interval (including but not limited to quinidine, amiodarone, pimozide, halofantrine, cisapride, citalopram, mizolastin, moxifloxacin, erythromycin). Clinical monitoring may also be required (see WARNINGS AND PRECAUTIONS).

Observed interactions to be considered

Beta-blockers

Additive effects leading to bradycardia (which may result in syncope) have been reported with the combined use of various beta-blockers (including atenolol) and rivastigmine. Cardio-selective beta-blockers are expected to be associated with the greatest risk, but reports have also been received in patients using other beta-blockers.

Nicotine

A population pharmacokinetic analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% in patients with Alzheimer's dementia (n=75 smokers and 549 non-smokers) following rivastigmine oral capsule doses of up to 12 mg/day.

Interactions with commonly used concomitant drugs

No pharmacokinetic interaction was observed between oral rivastigmine 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 oral rivastigmine. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and oral rivastigmine.

Concomitant administration of rivastigmine with commonly prescribed medications, such as antacids, antiemetics, antidiabetics, centrally acting antihypertensives, β-blockers, calcium channel blockers, inotropic drugs, antianginals, non-steroidal anti-inflammatory agents, oestrogens, analgesics, benzodiazepines, and antihistamines, was not associated with an alteration in the kinetics of rivastigmine or an increased risk of clinically relevant untoward effects.

According to its metabolism, metabolic drug interactions appear unlikely, although rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other drugs.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

In pregnant animals, rivastigmine and/or metabolites crossed the placenta. It is not known if this occurs in humans. No clinical data on exposed pregnancies are available. No effects on fertility or embryofoetal development were observed in rats and rabbits, except at doses related to maternal toxicity. In peri/postnatal studies in rats, an increased gestation time was observed. Rivastigmine should not be used during pregnancy unless clearly necessary.

Lactation

It is not known if rivastigmine is transferred into human milk. In animals, rivastigmine and/or metabolites were transferred in breast milk. Therefore, patients on rivastigmine should not breast-feed.

Females and males of reproductive potential

There is no information available on the effects of rivastigmine in women of child-bearing potential.

Infertility

There is no information available on the effects of rivastigmine on human fertility. In male and female rats, no adverse effects of rivastigmine were observed on fertility or reproductive performance of either the parent generation or the offspring of the parents.

OVERDOSAGE

Symptoms

Most cases of accidental overdose of oral rivastigmine have not been associated with any clinical signs or symptoms and almost all the patients concerned continued rivastigmine

treatment. Where symptoms have occurred, they have included nausea, vomiting, diarrhoea, abdominal pain, dizziness, tremor, headache, somnolence, bradycardia, confusional state, hyperhidrosis, hypertension, hallucinations, and malaise. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, and convulsions. Muscle weakness is a possibility and may result in death if respiratory muscles are involved. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur.

Overdose with Exelon patches resulting from misuse/medication errors (application of multiple patches at a time) has been reported in the post-marketing setting and rarely in clinical trials. Fatal outcome has been rarely reported with rivastigmine overdose and the relationship to rivastigmine was unclear. Symptoms of overdose and outcome vary from patient to patient and the severity of the outcome is not predictably related to the amount of the overdose.

Treatment

As rivastigmine has a plasma half-life of about 3.4 hours and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose all Exelon transdermal patches should be immediately removed, and no further patch should be applied for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment for other adverse events should be given as necessary.

In massive overdose, atropine can be used. An initial dose of 0.03 mg/kg intravenous atropine sulfate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: anticholinesterases, ATC code: N06DA03

Mechanism of action/ Pharmacodynamics (PD)

Rivastigmine is an acetyl- and butyryl-cholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurons. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits associated with Alzheimer's Disease.

Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes. In healthy young men, an oral 3.0 mg dose decreases acetylcholinesterase (AChE) activity in cerebro spinal fluid (CSF) by approximately 40% within the first 1.5 hours after administration. Activity of the enzyme returns to baseline levels about 9 hours after the maximum inhibitory effect has been achieved. In patients with Alzheimer's Disease (AD), inhibition of acetylcholinesterase in CSF by oral rivastigmine was

dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of BuChE activity in CSF of 14 AD patients treated by oral rivastigmine was similar to that of AChE.

Pharmacokinetics

Absorption

Absorption of rivastigmine from Exelon transdermal patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5 to 1 hour. C_{max} is reached after 10 to 16 hours. After the peak, plasma concentrations slowly decrease over the remainder of the 24-hour period of application. With multiple dosing (such as at steady state), after the previous patch is replaced with a new one, plasma concentrations initially decrease slowly for about 40 min on average, until absorption from the newly applied patch becomes faster than the elimination, and plasma levels begin to rise again to reach a new peak at approximately 8 hours. At steady state, trough levels are approximately 50% of peak levels, in contrast to oral administration, with which concentrations fall off to virtually zero between doses. Although less pronounced than with the oral formulation, exposure to rivastigmine (C_{max} and AUC) increased over-proportionally by a factor of 2.6 when escalating from 4.6mg/24 h to 9.5mg/24 h. The fluctuation index (FI), a measure of the relative difference between peak and trough concentrations ((C_{max} to C_{min})/C_{avg}), was 0.58 for Exelon 4.6/24 h transdermal patches and 0.77 for Exelon 9.5mg/24 h transdermal patches, thus demonstrating a much smaller fluctuation between trough and peak concentrations than for the oral formulation (FI = 3.96 (6mg/day) and 4.15 (12mg/day)).

The dose of rivastigmine released from the transdermal patch over 24 hours (mg/24h) cannot be directly equated to the amount (mg) of rivastigmine contained in a capsule with respect to plasma concentration produced over 24 hours.

The single dose study inter-subject in rivastigmine pharmacokinetic parameters (normalised to dose/kg bodyweight) was 43% (C_{max}) and 49% (AUC_{0-24h}) after transdermal administration versus 74% and 103%, respectively, after the oral form. The inter-subject variability in a steady-state study in Alzheimer's dementia was most 45% (C_{max}) and 43% (AUC_{0-24h}) after use of the transdermal patch, and 71% and 73%, respectively, after administration of the oral form.

A relationship between drug exposure at steady state (rivastigmine and metabolite NAP226-90) and bodyweight was observed in Alzheimer's dementia patients. 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. The effect of bodyweight on drug exposure suggests special attention to patients with very low body weight during up-titration (see WARNINGS AND PRECAUTIONS).

Exposure (AUC_{∞}) to rivastigmine (and metabolite NAP266-90) was highest when the patch was applied to the upper back, chest, or upper arm and approximately 20-30% lower when applied to the abdomen or thigh.

There was no relevant accumulation of rivastigmine or the metabolite NAP226-90 in plasma in patients with Alzheimer's disease, except that plasma levels were higher on the second day of transdermal patch therapy than on the first.

Distribution

Rivastigmine is weakly bound to plasma proteins (approximately 40%). It readily crosses the blood-brain barrier and has an apparent volume of distribution in the range of 1.8 to 2.7 l/kg.

Metabolism

Rivastigmine is rapidly and extensively metabolized with an apparent elimination half-life in plasma of approximately 3.4 hours after removal of the transdermal patch. Elimination was absorption rate limited (flip-flop kinetics), which explains the longer $t_{½}$ after patch (3.4 h) versus oral or i.v. administrations (1.4 to 1.7 h). Metabolism is primarily via cholinesterase-mediated hydrolysis to the metabolite NAP226-90. *In vitro*, this metabolite shows minimal inhibition of acetylcholinesterase (<10%). Based on *in vitro* studies, no pharmacokinetic drug interactions are expected with drugs metabolized by the following cytochrome isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6. Based on evidence from animal studies, the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Total plasma clearance of rivastigmine was approximately 130 liters/h after a 0.2 mg intravenous dose and decreased to 70 liters/h after a 2.7 mg intravenous dose, which is consistent with the non-linear, over-proportional pharmacokinetics of rivastigmine due to saturation of its elimination.

The metabolite-to-parent AUC_{∞} ratio was around 0.7 after patch versus 3.5 after oral administration, indicating that much less metabolism occurred after dermal compared to oral treatment. Less NAP226-90 is formed following application of the transdermal patch, presumably because of the lack of pre-systemic (hepatic first pass) metabolism, in contrast to oral administration.

Elimination

Unchanged rivastigmine is found in trace amounts in the urine; renal excretion of the metabolites is the major route of elimination after transdermal patch administation. Following administration of oral ^{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 faeces.

Elderly subjects

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

Subjects with hepatic impairment

No study was conducted with the Exelon transdermal patches in subjects with hepatic impairment. After oral administration, the C_{max} of rivastigmine was approximately 60% higher and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects. Following a single 3-mg oral dose or multiple 6-mg twice a day oral doses, the mean oral clearance of rivastigmine was approximately 60 to 65% lower in mild (n=7, Child-Pugh score 5 to 6) and moderate (n=3, Child-Pugh score 7 to 9) hepatically impaired patients (n=10, biopsy proven) than in healthy subjects (n=10). These pharmacokinetic changes had no effect on either the incidence or severity of adverse effects

(see sections DOSAGE REGIMEN AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Subjects with renal impairment

No study was conducted with the Exelon transdermal patches in subjects with renal impairment. Based on population analysis creatinine clearance did not show any clear effect on steady state concentrations of rivastigmine or its metabolite. No dosage adjustment is necessary in patients with renal impairment (see section DOSAGE REGIMEN AND ADMINISTRATION).

CLINICAL STUDIES

Clinical studies in Alzheimer's Dementia

The efficacy of Exelon transdermal patches (10, 15 and 20) in patients with mild to moderately severe dementia of the Alzheimer's type has been demonstrated in a 24-week double-blind, placebo-controlled core study and its open-label extension phase and in a 48-week double blind active comparator study.

The efficacy of Exelon 13.3mg/24h in patients with severe dementia of the Alzheimer's type has been demonstrated in a 24-week double-blind study.

Mild to moderate Alzheimer's dementia

24-week controlled studies

Patients involved in a study had an MMSE (Mini-Mental State Examination) score of 10 to 20. Efficacy was established by the use of independent, domain-specific assessment tools which were applied at regular intervals during the 24-week treatment period. These include the ADAS-Cog (a performance-based measure of cognition) and the ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change: a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the ADCS-ADL (a caregiver-rated assessment of the activities of daily living including personal hygiene, feeding, dressing, household chores such as shopping, retention of ability to orient oneself to surroundings as well as involvement in activities related to finances). The 24-week results for the three assessment tools are summarised in Table 4.

Table 4 24-week results for the three assessment tools in patients with mild to moderate Alzheimer's dementia

	Exelon Transdermal patches 9.5mg/24h	**Exelon** capsule 12 mg/day	**Placebo**
ITT-LOCF population	N = 251	N = 256	N = 282
ADAS-Cog	(n=248)	(n=253)	(n=281)

Mean baseline ± SD	27.0 ±10.3	27.9 ± 9.4	28.6 ± 9.9
Mean change at week 24 ± SD	-0.6 ± 6.4	-0.6 ± 6.2	1.0 ± 6.8
p-value versus placebo	0.005*[1]	0.003*[1]	
ADCS-CGIC			
	(n=248)	(n=253)	(n=278)
Mean score ± SD	3.9 ± 1.20	3.9 ± 1.25	4.2 ± 1.26
p-value versus placebo	0.010*[2]	0.009*[2]	
ADCS-ADL			
	(n=247)	(n=254)	(n=281)
Mean baseline ± SD	50.1 ± 16.3	49.3 ± 15.8	49.2 ± 16.0
Mean change at week 24 ± SD	-0.1 ± 9.1	-0.5 ± 9.5	-2.3 ± 9.4
p-value versus placebo	0.013*[1]	0.039*[1]	

* p≤0.05 versus placebo

ITT: Intent-To-Treat; LOCF: Last Observation Carried Forward

[1] Based on ANCOVA with treatment and country as factors and baseline value as a covariate. Negative ADAS-Cog changes indicate improvement. Positive ADCS-ADL changes indicate improvement.

[2] Based on CMH test (van Elteren test) blocking for country. ADCS-CGIC scores <4 indicate improvement.

The results for clinically relevant responders from the 24-week study are provided in Table 5. Clinically relevant improvement was defined a priori as at least 4-point improvement on the ADAS-Cog, no worsening on the ADCS-CGIC, and no worsening on the ADCS-ADL.

Table 5 Results for clinically relevant responders from the 24-week placebo-controlled study in patients with mild to moderate Alzheimer's dementia

	Patients with Clinically Significant Response (%)		
	Exelon transdermal patches 9.5mg/24h	Exelon capsule 12mg/day	Placebo
ITT- LOCF population	N = 251	N = 256	N = 282
At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL	17.4*	19.0**	10.5
p-value versus placebo	0.037*	0.004*	

*p<0.05, **p<0.01 versus placebo

As suggested by compartmental modeling, 9.5mg/24 h transdermal patches exhibited exposure similar to that provided by an oral dose of 12 mg/day. Similar results were observed in separately conducted controlled studies in Chinese and Japanese patients with mild to moderately severe Alzheimer's dementia.

48-week active comparator-controlled study

Patients involved in the active comparator-controlled study had an initial baseline MMSE (Mini-Mental State Examination) score of 10 to 24. The study was designed to compare the efficacy of the Exelon Patch 15 versus the Exelon Patch 10 during a 48-week double blind treatment phase in Alzheimer's disease patients who demonstrated functional and cognitive decline after an initial 24 to 48-week open-label treatment phase while on a maintenance dose

of Exelon Patch 10. 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. Efficacy was established by the use of independent, domain-specific assessment tools which were applied at regular intervals during the 48 week treatment period. These include the ADAS-Cog (a performance-based measure of cognition) and the ADCS-instrumental ADL (a subscale from the ADCS-ADL activities of daily living scale assessing instrumental activities which are thought to involve more complex cognitive activities and represent clinically meaningful functional activities of daily living, which include maintaining finances, meal preparation, shopping, ability to orient oneself to surroundings, able to be left unattended, etc.). The 48-week results for the two assessment tools are summarized in Table 6.

Table 6 Mean change from double-blind baseline in ADAS-Cog and ADCS-IADL scores over time in patients with mild to moderate Alzheimer's dementia

Population / Visit		Exelon Patch 15 N = 265	Exelon Patch 10 N = 271	Exelon Patch 15 - Exelon Patch 10		
		Mean	Mean	DLSM	95% CI	p-value
ADAS-Cog		(n=264)	(n=268)			
LOCF	Baseline	34.4	34.9			
DB-week 24	Value	35.4	37.1			
	Change	1.0	2.2	-1.3	(-2.5, -0.2)	0.027*
DB-week 48	Value	38.5	39.7			
	Change	4.1	4.9	-0.8	(-2.1, 0.5)	0.227
ADCS-IADL		(n=265)	(n=271)			
LOCF	Baseline	27.5	25.8			
Week 24	Value	26.0	22.9			
	Change	-1.5	-2.8	1.7	(0.5, 2.9)	0.005*
Week 48	Value	23.1	19.6			
	Change	-4.4	-6.2	2.2	(0.8, 3.6)	0.002*

ANCOVA - analysis of covariance, CI – confidence interval, DB – double blind

DLSM – difference in least square means, LOCF – Last Observation Carried Forward.

ADAS-cog scores: A negative difference in DLSM indicates greater improvement in Exelon 15 cm^2 as compared to Exelon 10 cm^2

ADCS-IADL scores: 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 and the corresponding visit.

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

* $p < 0.05$

Severe Alzheimer's dementia

24-week controlled study

Patients involved in the controlled study had at baseline an MMSE (Mini-Mental State Examination) score of ≥3 and ≤12. The study was designed to compare the efficacy of Exelon Patch 15 versus Exelon Patch 5 during a 24-week double blind treatment phase in severe Alzheimer's disease. Efficacy was established by the use of independent, domain-specific assessment tools. These include the SIB, the ADCS-ADL-SIV and the ADCS-CGIC.
The SIB: the Severe Impairment Battery is a 40-item scale with a range of possible scores from 0 to 100, with higher scores reflecting higher levels of cognitive function.
The ADCS-ADL-SIV: the Alzheimer's Disease Cooperative Study Activity of Daily Living-Severe Impairment Version is a caregiver-based scale consisting of 19 items designed to assess the patient's performance of both basic and instrumental activities of daily living, which had been used in several studies in moderate to severe Alzheimer's dementia. The total score ranges from 0 – 54, with higher scores indicating better function.
The ADCS-CGIC: the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change is a comprehensive global assessment of the patient by the physician incorporating caregiver input.

The 24-week results for the three assessment tools are summarized in Table 7.

Table 7 24-week results for the three assessment tools in patients with severe Alzheimer's dementia

MFAS-LOCF population	**Exelon Patch 15** N = 338	**Exelon Patch 5** N = 335
SIB		
	(n=336)	(n=334)
Mean baseline ± SD	69.3 ± 21.54	68.3 ± 22.79
Mean change at week 24 ± SD	-1.7 ± 0.79	-6.6 ± 0.79
LS Means difference (95% CI)[1]	4.9 (2.80, 6.95)	
p-value[1]	<0.0001*	
ADCS-ADL-SIV		
	(n=333)	(n=319)
Mean baseline ± SD	29.7 ± 11.29	29.1 ±11.94
Mean change at week 24 ± SD	-2.4 ± 0.41	-3.6 ± 0.42
LS Means difference (95% CI)[1]	1.2 (0.16, 2.32)	
p-value[1]	0.0247*	
ADCS-CGIC		
	(n=313)	(n=315)
No change or improvement n (%)	184 (58.8)	143 (45.4)
Difference (95% CI)[2]	13.4 (5.65, 21.13)	
p-value[3]	0.0013*	

* p≤0.05
MFAS: Modified Full Analysis Set.
LOCF: Last Observation Carried Forward.
LS: Least Squares.
ADCS-CGIC: refers to the number (percent) of patients with no change or improvement in total score.
[1] Obtained from an ANCOVA model with treatment and pooled center as factors, and baseline score (SIB or ADCS-ADL-SIV, respectively) as a covariate.
[2] 95% confidence interval (CI) based on the normal approximation.
[3] From Cochran-Mantel-Haenszel (CMH) chi-square test, adjusting for pooled center.

Clinical studies in dementia associated with Parkinson's disease

The efficacy of Exelon capsules in patients with dementia associated with Parkinson's disease was demonstrated in a 24-week multicentre, double-blind, placebo-controlled core study and its 24-week open-label extension phase. Patients involved in this study were to have an MMSE (Mini-Mental State Examination) score at screening of 10 to 24. Efficacy has been established by the use of two independent scales which were assessed at regular intervals during a 6-month treatment period: the ADAS-Cog, a measure of cognition, and the global measure ADCS-CGIC.

The efficacy of Exelon transdermal patch in dementia associated with Parkinson's disease was investigated in an open- label safety study. Patients involved in this study were to have an MMSE score at screening of 10 to 26. Efficacy was evaluated by the use of two independent scales which were assessed at regular intervals. These include the MDRS (Mattis Dementia Rating Scale, a performance-based measure of cognition) and the ADCS-ADL.

The 24-week results for the two scales are summarized in Table 8.

Table 8 24-week results for MDRS and ADCS-ADL scales

ITT-LOCF population	**Exelon Patch 10 (9.5 mg/24 h)** N = 273
MDRS	
	(n=273)
Mean baseline ± SD	109.4 ± 19.6
Mean change at week 24 ± SD	4.4 ± 12.9[1]
ADCS-ADL	
	(n=270)
Mean baseline ± SD	50.1 ± 17.0
Mean change at week 24 ± SD	-1.5 ± 10.9[1]

[1]Positive MDRS and ADCS-ADL changes indicate improvement.

NON-CLINICAL SAFETY DATA

Oral and topical repeated-dose toxicity studies in mice, rats, rabbits, dogs and minipigs revealed only effects associated with an exaggerated pharmacological action. No target organ toxicity was observed. Oral and topical dosing in animal studies was limited due to the sensitivity of the animal models used.

Rivastigmine was not mutagenic in a standard battery of *in* vitro and *in* vivo tests, except in a chromosomal aberration test in human peripheral lymphocytes at a dose exceeding 10^4 times

the foreseen clinical exposure. The *in* vivo micronucleus test was negative. In addition, the major metabolite NAP226-90 did not induce structural chromosome aberrations in an *in vitro* test indicating that the compound has no genotoxic potential.

No evidence of carcinogenicity was found in oral and topical studies in mice and in an oral study in rats at the maximum tolerated dose. The exposure to rivastigmine and its metabolites was approximately equivalent to human exposure with highest doses of rivastigmine capsules and transdermal patches.

In animals, rivastigmine crosses the placenta and is excreted into milk. Oral studies in pregnant rats and rabbits gave no indication of teratogenic potential on the part of rivastigmine. Specific dermal studies in pregnant animals have not been conducted.

Rivastigmine transdermal patches were not phototoxic and considered to be a non-sensitizer. In some other dermal toxicity studies, a mild irritant effect on the skin of laboratory animals, including controls, was observed. This may indicate a potential for Exelon transdermal patches to induce mild erythema in patients. When administered to rabbit eyes in primary eye irritation studies, rivastigmine caused reddening and swelling of the conjunctiva, corneal opacities and miosis which persisted for 7 days. Therefore, the patient/caregiver should avoid contact with the eyes after handling of the patch (see WARNINGS AND PRECAUTIONS).

INCOMPATIBILITIES

To prevent interference with the adhesive properties of the transdermal patch, no cream, lotion, or powder should be applied to the skin area where the Exelon transdermal patch is to be applied.

STORAGE

See folding box

Exelon Patch should not be used after the date marked “EXP” on the pack

Exelon Patch must be kept out of the reach and sight of children.

PACK SIZE

Box of 30 patches

INSTRUCTIONS FOR USE AND HANDLING

IMPORTANT: Only one patch should be worn at a time. You must remove the previous day’s Exelon Patch **before** applying a new one. Do not cut the patch into pieces.

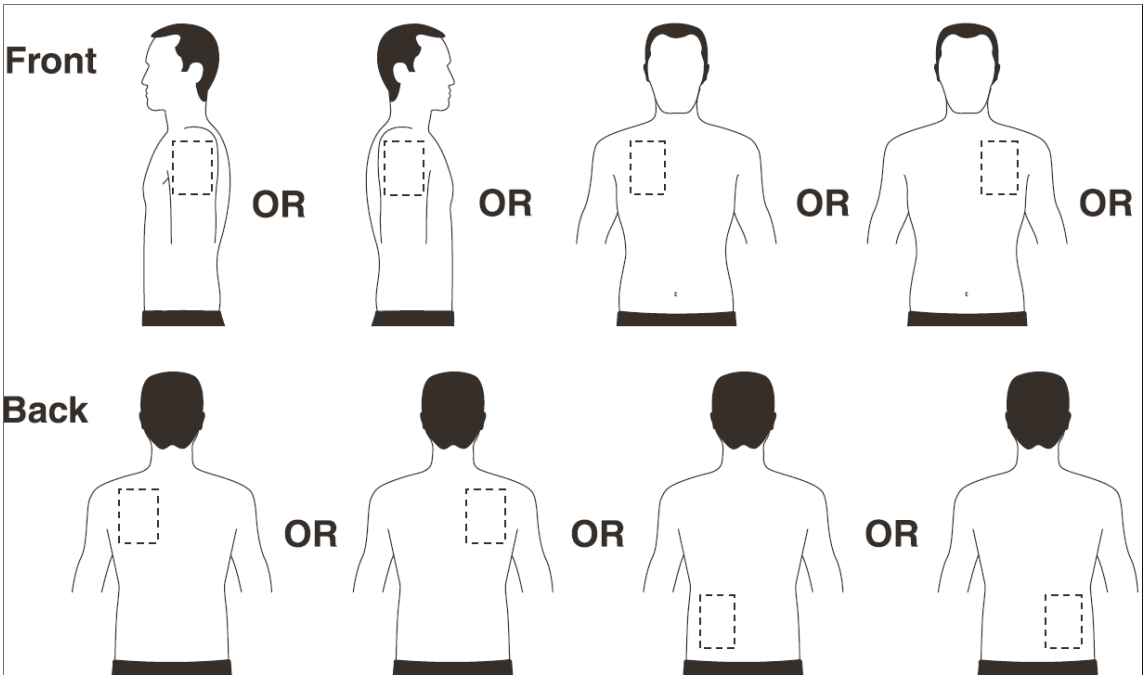
Where to apply Exelon Patch

Apply the patch to the upper or lower back, upper arm or chest. Avoid places where the patch can be rubbed off by tight clothing.

- 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.



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.

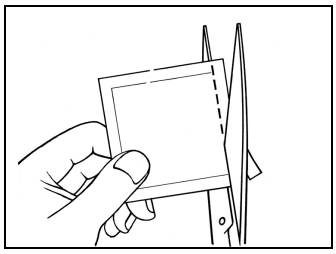
How to apply Exelon Patch

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.

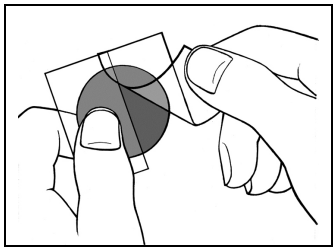
Every 24 hours, please gently remove any existing Exelon patch before putting on a new one. Having multiple patches on your body could expose you to an excessive amount of this medicine which could be potentially dangerous.

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

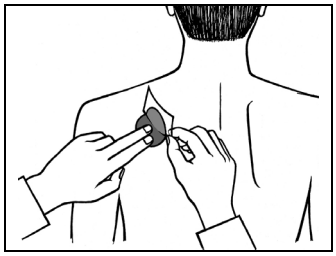
  Tear or cut the sachet or at the notch and remove the patch.



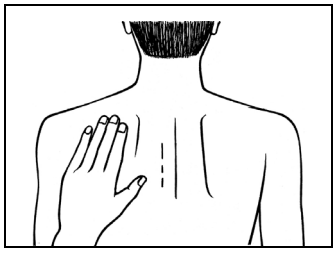
- A protective liner covers the adhesive side of the patch.
  Peel off one side of the protective liner and do not touch the sticky part of the patch with the fingers.



- 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.

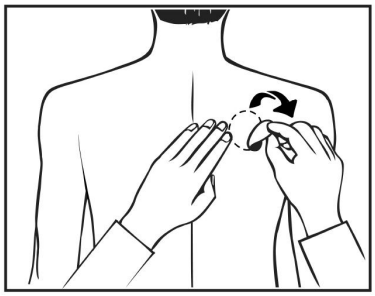


- If it helps you, you may write (e.g. the day of the week) on the Exelon Patch with a thin ball point pen.

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.

Country-Specific Package Leaflet

® = registered trademark

Novartis Pharma AG, Basel, Switzerland