

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

EXELON® rivastigmine 5 cm², 10 cm², 15 cm² and 20 cm² Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Exelon Patch area (cm ²)	Rivastigmine base dose load	Rivastigmine base <i>in vivo</i> release rates
5	9 mg	4.6 mg/24 hr
10	18 mg	9.5 mg/24 hr
15	27 mg	13.3 mg/24 hr
20	36 mg	17.4 mg/24 hr

3 PHARMACEUTICAL FORM

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

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

- “AMCX” for Exelon Patch 5
- “BHDI” for Exelon Patch 10
- “CNFU” for Exelon Patch 15
- “DSEN” for Exelon Patch 20

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of patients with:

- Mild to moderately severe dementia of the Alzheimer’s type (also termed probable Alzheimer’s Disease or Alzheimer’s Disease)
- Severe dementia of the Alzheimer’s type.

4.2 Dose and method of administration

Dosage

Mild to moderately severe dementia of the Alzheimer’s type

Initial dose and dose titration to the effective dose:

Treatment is started with Exelon Patch 5 once a day.

After a minimum of four weeks of treatment and if well tolerated, this dose should be increased to Exelon Patch 10, which is the recommended effective dose to be continued for as long as a therapeutic benefit for the patient exists.

Individual responses to rivastigmine may vary and some patients may derive additional benefit from higher doses. Subsequent increases to Exelon Patch 15 and then to Exelon Patch 20 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.

Severe dementia of the Alzheimer's type

Initial dose and dose titration to the effective dose:

Treatment is started with Exelon Patch 5 once a day. Subsequently the dose should be increased to Exelon Patch 10 and then to Exelon Patch 15 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 and/or worsening of existing extrapyramidal symptoms (e.g. tremor) are observed until these adverse effects resolve. Patch treatment can be resumed at the same dose if treatment is not interrupted for more than three days. Otherwise treatment should be re-initiated with Exelon Patch 5.

If adverse effects persist on re-initiation of therapy, the dose should be temporarily reduced to the previous well-tolerated dose.

Switching from capsules:

Patients treated with Exelon capsules may be switched to Exelon patches as follows:

- A patient who is on a dose of < 6 mg per day oral rivastigmine can be switched to Exelon Patch 5.
- A patient who is on a dose of 6 to 12 mg per day oral rivastigmine may be directly switched to Exelon Patch 10.

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

Method of administration

Exelon 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. The patch should be replaced with 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 Section 4.4 Special warnings and precautions for use and Section 4.9 Overdose).

The patch should not be applied to skin that is red, irritated or cut. It is recommended to change the application site daily to avoid potential irritation, although consecutive patches can be applied to the same anatomic site (e.g. another spot on the upper back).

The 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, on 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. Patients and caregivers should be instructed accordingly.

Immediately after removing the patch, patients or caregivers must wash their hands with soap and water. In case of contact with eyes or if the eyes become red after handling the patch, patients or caregivers must rinse the area 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 and may be more likely to discontinue due to adverse events. Particular caution should be exercised in titrating and monitoring these patients for adverse reactions (e.g. excessive nausea or vomiting) and consider reducing the dose if such adverse reactions develop (see Section 4.4 Special warnings and precautions for use).

Paediatric patients

Rivastigmine is not recommended for use in children and adolescents (aged below 18 years).

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 might experience more adverse events. Particular caution should be exercised in titrating these patients above the recommended maintenance dose of Exelon Patch 10 (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetics properties).

Renal impairment

No dose adjustment is necessary for patients with renal impairment (see Section 5 PHARMACEUTICAL PROPERTIES – Section 5.2 Pharmacokinetics (PK) properties).

4.3 Contraindications

The use of Exelon is contraindicated in patients with:

- known hypersensitivity to rivastigmine, other carbamate derivatives or other ingredients of the formulation (see Section 6.1 List of Excipients).
- previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine transdermal patch (see Section 4.4 Special warnings and precautions for use – Application site reactions and skin reactions).

4.4 Special warnings and precautions for use

Medication misuse and dosing errors resulting in overdose

Medication misuse and dosing errors with Exelon patches have resulted in serious adverse reactions; some cases have required hospitalisation, and rarely led to death

(see “Section 4.9 Overdose”). 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 patch (see “Section 4.2 Dose and method of administration”).

Gastrointestinal disorders

The incidence and severity of adverse reactions generally increase with increasing doses, particularly at dose changes. If treatment is interrupted for more than three days, it should be re-initiated with Exelon Patch 5.

Gastrointestinal disorders such as nausea, vomiting and diarrhoea may occur when initiating treatment and/or increasing the dose. They may respond to a dose reduction. In other cases, use of Exelon patches has been discontinued. 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 Section 4.8 Undesirable effects).

Weight loss

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

Other adverse reactions from increased cholinergic activity

As with other cholinergic substances care must be taken when prescribing Exelon patches to patients:

- with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see Section 4.8 Undesirable effects).
- with active gastric or duodenal ulcers or patients predisposed to these conditions because gastric acid secretions may be increased.
- predisposed to urinary obstruction and seizures because cholinomimetics may induce or exacerbate these diseases.
- with a history of asthma or obstructive pulmonary disease.

Like other cholinomimetics, rivastigmine may induce or exacerbate extrapyramidal symptoms.

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 4.8 Undesirable effects – Application site reactions). These reactions are not in themselves an indication of sensitisation. 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 Sections 4.3 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 sensitised 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 4.3 Contraindications). Patients and caregivers should be instructed accordingly.

Special populations

Patients with body weight below 50 kg

Patients with body mass below 50 kg may experience more adverse reactions and may be more likely to discontinue due to adverse events. 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 4.2 Dose and method of administration).

Paediatric patients

Rivastigmine is not recommended for use in children and adolescents (aged below 18 years).

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. Particular caution should be exercised in titrating these patients (see Section 4.2 Dose and method of administration and Section 5 PHARMACEUTICAL PROPERTIES – Section 5.2 Pharmacokinetics (KP) properties).

4.5 Interaction with other medicines and other forms of interaction

No specific interaction studies have been conducted with Exelon patches.

Rivastigmine is metabolised mainly through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes thus, no pharmacokinetic interactions are anticipated with other drugs metabolised by these enzymes.

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.

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. Cardioselective beta-blockers are expected to be associated with the greatest risk, but reports have also been received in patients using other beta-blockers.

Interaction with 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 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 rivastigmine. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and rivastigmine.

Concomitant administration of rivastigmine with commonly prescribed medications, such as antacids, antiemetics, antidiabetics, centrally acting antihypertensives, calcium channel blockers, inotropic drugs, antianginals, non-steroidal anti-inflammatory drugs, 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.

4.6 Fertility, Pregnancy and lactation

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

Pregnancy

In pregnant animals, rivastigmine and/or metabolites crossed the placenta. It is not known if this occurs in humans. In animal studies, rivastigmine was not teratogenic. However, the safety of Exelon in human pregnancy has not been established, and it should only be given to pregnant women if the potential benefit outweighs the potential risk for the foetus.

Lactation

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

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. There is no information available on the effects of rivastigmine on human fertility

4.7 Effects on ability to drive and use machines

Alzheimer's disease dementia may cause gradual impairment of driving performance or compromise the ability to use machinery. Rivastigmine may induce dizziness and somnolence, mainly when initiating treatment or increasing the dose. 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.

4.8 Undesirable effects

The overall incidence of adverse events in patients treated with Exelon Patch 10 was lower than the rate in patients who received Exelon capsule treatment. Nausea and vomiting were the most common adverse events in patients who received active treatment, and occurred at similar rates in both Exelon Patch 20 and capsule groups. However, the rates of both of these events were substantially lower with Exelon Patch 10 group. The most commonly reported adverse drug reactions are gastrointestinal including nausea and vomiting, especially during titration.

Adverse reactions in Table 1 are ranked under headings of frequency, the most frequent first, using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), including isolated reports.

Table 1: Adverse drug reactions reported in 2687 patients with Alzheimer's dementia treated for 24 weeks to 48 weeks in randomised 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:	Dizziness, headache
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	
Uncommon:	Hyperhidrosis
General disorders and administration site conditions	
Common:	Application site reactions, application site erythema**, application site pruritus, application site oedema**, fatigue, asthenia
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”.

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, rash, erythema, urticaria, blister, dermatitis allergic
Very rarely reported	tachycardia, atrioventricular block, atrial fibrillation, pancreatitis, seizure. Worsening of Parkinson’s disease has been observed in patients with Parkinson’s disease who were treated with Exelon patches
Frequency not known	hepatitis, restlessness, sick sinus syndrome, 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
Uncommon	abnormal liver function tests
Common	confusion

Information from clinical trials in patients with Alzheimer’s dementia treated with Exelon patches

The adverse drug reactions in Table 2 were reported in patients with mild to moderate Alzheimer’s dementia treated with Exelon patches.

The adverse drug reactions in Table 3 were reported in patients with severe Alzheimer’s dementia treated with Exelon Patch 15.

Table 2: Adverse drug reactions ($\geq 2\%$ in all Exelon Patch groups) from the 24-week double-blind placebo controlled clinical trial conducted with Exelon patches in patients with mild to moderate Alzheimer’s dementia

	Exelon Patch 10 group n (%)	Exelon Patch 20 group n (%)	Exelon capsules 12 mg/day n (%)	Placebo n (%)	All Exelon patches group n (%)
Total patients studied	291	303	294	302	594
Total patients with AE(s)	147 (50.5)	200 (66.0)	186 (63.3)	139 (46.0)	347(58.4)
Nausea	21 (7.2)	64 (21.1)	68 (23.1)	15 (5.0)	85(14.3)
Vomiting	18 (6.2)	57 (18.8)	50 (17.0)	10 (3.3)	75(12.6)
Diarrhoea	18 (6.2)	31 (10.2)	16 (5.4)	10 (3.3)	49(8.2)

Weight decreased	8 (2.7)	23 (7.6)	16 (5.4)	4 (1.3)	31(5.2)
Dizziness	7 (2.4)	21 (6.9)	22 (7.5)	7 (2.3)	28(4.7)
Decreased appetite	2 (0.7)	15 (5.0)	12 (4.1)	3 (1.0)	17(2.9)
Headache	10 (3.4)	13 (4.3)	18 (6.1)	5 (1.7)	23(3.9)
Anorexia	7 (2.4)	12 (4.0)	14 (4.8)	3 (1.0)	19(3.2)
Depression	11 (3.8)	12 (4.0)	13 (4.4)	4 (1.3)	23(3.9)
Insomnia	4 (1.4)	12 (4.0)	6 (2.0)	6 (2.0)	16(2.7)
Abdominal pain	7 (2.4)	11 (3.6)	4 (1.4)	2 (0.7)	18(3.0)
Asthenia	5 (1.7)	9 (3.0)	17 (5.8)	3 (1.0)	14(2.4)
Anxiety	9 (3.1)	8 (2.6)	5 (1.7)	4 (1.3)	17(2.9)
Fatigue	5 (1.7)	7 (2.3)	2 (0.7)	4 (1.3)	12(2.0)

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	Patch 15 group n (%)	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	127 (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. Skin irritation, when observed, was mostly slight or mild in severity and was rated

as severe in ≤ 2.2 % of Exelon Patch patients in a double-blind controlled study and in ≤ 3.7 % of Exelon Patch patients in a double-blind controlled study in Japanese patients.

See Section 4.4 Special warnings and precautions for use – Skin application site and skin reactions.

Reporting of suspected adverse reactions - Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Symptoms

Most cases of accidental overdosage have not been associated with any clinical signs or symptoms and almost all of 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 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 duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose all Exelon 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 i.v atropine sulphate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

For advice on the management of overdose please contact the National Poisons Centre 1800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action/Pharmacodynamics (PD)

Pharmacotherapeutic group: brain-selective cholinesterase inhibitor; ATC-code: N06DA03.

Pathological changes in dementia such as Alzheimer's Disease involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are known to be involved in attention, learning and memory and other cognitive processes. Rivastigmine, a brain-selective acetyl- and butyryl-cholinesterase inhibitor of the carbamate type, is thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurons. Data from animal studies indicate that rivastigmine selectively increases the availability of acetylcholine in the cortex and hippocampus. Thus, Exelon may have an ameliorative effect on cholinergic-mediated cognitive deficits associated with Alzheimer's Disease and with Parkinson's disease. In addition, there is some evidence that cholinesterase inhibition could slow the formation of amyloidogenic beta-amyloid-precursor protein (APP) fragments, and thus of amyloid plaques, which are one of the main pathological features of 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. Butyrylcholinesterase (BuChE) activity in CSF was transiently inhibited and was no longer different from baseline after 3.6 hours in healthy young volunteers. In patients with Alzheimer's Disease (AD), inhibition of acetylcholinesterase in CSF by rivastigmine was dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of BuChE activity in CSF of AD patients by rivastigmine was similar to that of AChE, with a change from baseline of more than 60% after 6 mg given twice daily. The effect of rivastigmine on AChE and BuChE activity in CSF was sustained after 12 months administration, the longest time studied. Statistically significant correlations were found between the degree of inhibition by rivastigmine of AChE and BuChE in the CSF and changes on a compound measure of cognitive performance in AD patients; however, only BuChE inhibition in CSF was significantly and consistently correlated with improvements in speed-, attention- and memory-related subtests.

CLINICAL STUDIES

Alzheimer's Dementia

The efficacy of Exelon 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.

Mild to Moderate Alzheimer's dementia

24-week placebo-controlled study

Patients involved in a placebo-controlled study had an MMSE (Mini-Mental State Examination) score of 10–20. 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), the ADCS-CGIC (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.

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

	Exelon Patch 10	Exelon Patch 20	Exelon capsule 12 mg/day	Placebo
ITT-LOCF population	N = 251	N = 264	N = 256	N = 282
ADAS-Cog	(n=248)	(n=262)	(n=253)	(n=281)
Mean baseline \pm SD	27.0 \pm 10.3	27.4 \pm 9.7	27.9 \pm 9.4	28.6 \pm 9.9
Mean change at week 24 \pm SD	-0.6 \pm 6.4	-1.6 \pm 6.5	-0.6 \pm 6.2	1.0 \pm 6.8
p-value versus placebo	0.005* ¹	<0.001* ¹	0.003* ¹	
ADCS-CGIC	(n=248)	(n=260)	(n=253)	(n=278)
Mean score \pm SD	3.9 \pm 1.20	4.0 \pm 1.27	3.9 \pm 1.25	4.2 \pm 1.26
p-value versus placebo	0.010* ²	0.054 ²	0.009* ²	
ADCS-ADL	(n=247)	(n=263)	(n=254)	(n=281)
Mean baseline \pm SD	50.1 \pm 16.3	47.6 \pm 15.7	49.3 \pm 15.8	49.2 \pm 16.0
Mean change at week 24 \pm SD	-0.1 \pm 9.1	0.0 \pm 11.6	-0.5 \pm 9.5	-2.3 \pm 9.4
p-value versus placebo	0.013* ¹	0.017* ¹	0.039* ¹	

* $p \leq 0.05$ 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.

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 Patch 10	Exelon Patch 20	Exelon capsule 12mg/day	Placebo
At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL	17.4*	20.2**	19.0**	10.5

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

Similar results were observed with Exelon Patch 10 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 10–24. 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 24-48 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.

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 SIB¹, the ADCS-ADL-SIV² and the

¹ Severe Impairment Battery (SIB) test is a 40-item scale with a range of possible scores from 0 to 100, with lower scores reflecting lower levels of cognitive function.

² Alzheimer’s Disease Cooperative Study Activity of Daily Living-Severe Impairment Version (ADCS-ADL-SIV) 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 lower scores indicating poorer function.

ADCS-CGIC³. The 24-week results for the three assessment tools are summarised in Table 7.

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		Patch 15 N = 265	Patch 10 N = 271	Patch 15 - Patch 10		
		Mean	Mean	DLSM	95% CI	p-value
ADAS-Cog LOCF		(n=264)	(n=268)			
	Baseline	34.4	34.9			
DB- week	Value	34.2	35.5	-0.9	(-2.0, 0.1)	0.091
	Change	-0.2	0.6			
	12					
DB- week	Value	35.4	37.1	-1.3	(-2.5, -0.2)	0.027*
	Change	1.0	2.2			
24						
DB- week	Value	38.5	39.7	-0.8	(-2.1, 0.5)	0.227
	Change	4.1	4.9			
48						
ADCS-IADL LOCF		(n=265)	(n=271)			
	Baseline	27.5	25.8			
Week 8	Value	27.3	25.0	0.8	(-0.2, 1.9)	0.114
	Change	-0.2	-0.8			
Week 12	Value	27.5	25.4	0.7	(-0.5, 1.8)	0.252
	Change	0.1	-0.4			
Week 16	Value	26.7	24.0	1.3	(0.2, 2.5)	0.025*
	Change	-0.7	-1.8			
Week 24	Value	26.0	22.9	1.7	(0.5, 2.9)	0.005*
	Change	-1.5	-2.8			
Week 32	Value	25.2	21.7	2.1	(0.9, 3.4)	<0.001*
	Change	-2.2	-4.0			
Week 48	Value	23.1	19.6	2.2	(0.8, 3.6)	0.002*
	Change	-4.4	-6.2			

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 cm² as compared to Exelon 10 cm²

ADCS-IADL scores: A positive difference in DLSM indicates greater improvement in Exelon 15 cm² as compared to Exelon 10 cm²

n = 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

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

	Exelon Patch 15	Exelon Patch 5
MFAS-LOCF population	N = 338	N = 335
SIB¹	(n=336)	(n=334)
Mean baseline ± SD	69.3 ± 21.54	68.3 ± 22.79

³ Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) is a comprehensive global assessment of the patient by the physician incorporating caregiver input.

Mean change at week 24 ± SD	-1.7 ± 0.79	-6.6 ± 0.79
LS Means difference (95% CI) ^[a]	4.9 (2.80, 6.95)	
p-value ^[a]	<0.0001*	
ADCS-ADL-SIV²	(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) ^[a]	1.2 (0.16, 2.32)	
p-value ^[a]	0.0247*	
ADCS-CGIC³	(n=313)	(n=315)
No change or improvement n (%)	184 (58.8)	143 (45.4)
Difference (95% CI) ^[b]	13.4 (5.65, 21.13)	
p-value ^[c]	0.0013*	

* p ≤ 0.05; MFAS: Modified Full Analysis Set; LOCF: Last Observation Carried Forward; ADCS-CGIC: number (percent) of patients with no change or improvement in total score; LS: Least Squares

^[a] Obtained from an ANCOVA model with treatment and pooled center as factors, and baseline score (SIB or ADCS-ADL-SIV, respectively) as a covariate

^[b] 95% confidence interval (CI) based on the normal approximation

^[c] From Cochran-Mantel-Haenszel (CMH) chi-square test, adjusting for pooled center.

5.2 Pharmacokinetic (PK) properties

Absorption:

Absorption of rivastigmine from Exelon patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5-1 hour. Concentrations then rise slowly and typically after 8 hours reach levels close to maximum, although maximum values (C_{max}) are often reached at later times (10-16 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 dosing, with which concentrations fall off to virtually zero between doses (see Figure 1). This time course of plasma concentrations is observed with all patch strengths (sizes) in the investigated range of Exelon Patch 5 to Exelon Patch 20. Although less pronounced than with the oral formulation, exposure to rivastigmine (C_{max} and AUC) increased over-proportionally with rising patch doses. Escalating from Exelon Patch 5 to Exelon Patch 20, the increase in rivastigmine AUC relative to the lowest dose of Exelon Patch 5 was 2.6, 4.9 and 7.8 fold for Exelon Patch 10, Exelon Patch 15 and Exelon Patch 20, respectively. The fluctuation index (FI), i.e. a measure of the relative difference between peak and trough concentrations ($(C_{max}-C_{min})/C_{avg}$), was in the range 0.57 to 0.77 for the patch, thus demonstrating a much smaller fluctuation between trough and peak concentrations than for the oral formulation (FI = 3.96 to 6.24). As determined by compartmental modelling the Exelon Patch 20 exhibited exposure (AUC_{24h}) in a typical patient equivalent to that which would be provided by an oral dose of about 9 to

10 mg twice daily (i.e. 18 to 20 mg/day), while Exelon Patch 10 exhibited exposure equivalent to that provided by an oral dose of about 6 mg twice daily (i.e. 12 mg/day).

Figure 1 Rivastigmine plasma concentrations following dermal 24-hour patch application

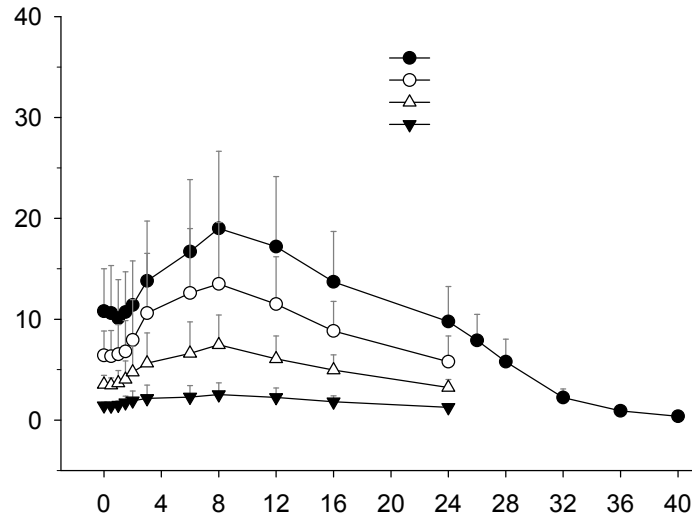
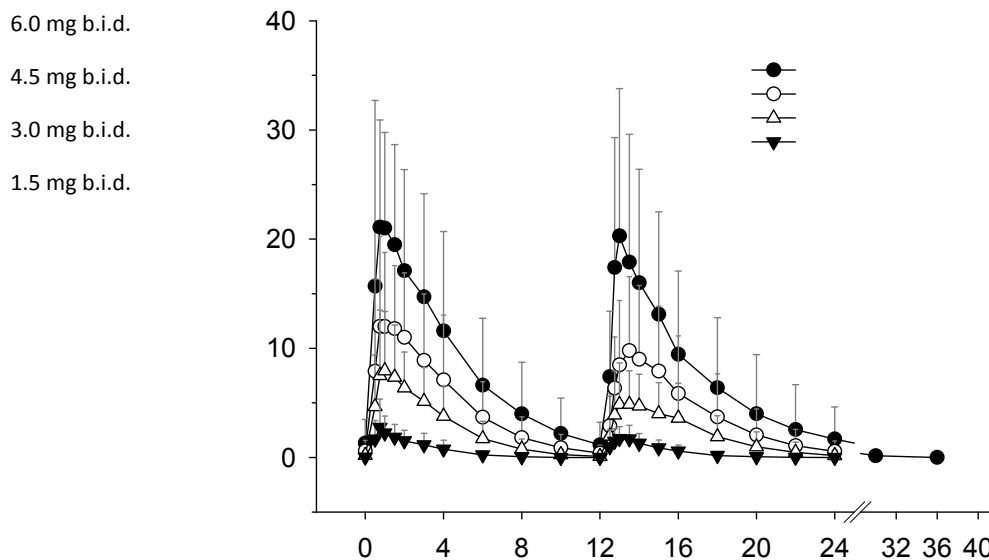


Figure 2 Rivastigmine plasma concentrations following oral (twice daily) capsule



In a single dose study directly comparing the patch versus oral administration, the inter-subject variability in rivastigmine pharmacokinetic parameters (normalised to dose/kg bodyweight) was 43% (C_{max}) and 49% (AUC_{0-24h}) after the patch versus 74% and 103%, respectively, after the oral capsule. Similarly, inter-subject variability in rivastigmine pharmacokinetic parameters was lower after the patch than after the oral capsule in a steady-state study in Alzheimer's dementia patients given repeated doses. The inter-

patient variability was at most 45% (C_{max}) and 43% (AUC_{0-24h}) after the patch, while 71% and 73%, respectively, after 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 Section 4.2 Dosage and method of administration).

Rivastigmine was well released from the transdermal system over a 24-hour dermal application with approximately 50% of the drug load released from the system. Exposure (AUC_{∞}) to rivastigmine (and metabolite NAP266-90) was highest when the patch was applied to the upper back, chest, or upper arm. Two other sites (abdomen and thigh) could be used if none of the three other sites is available, but the practitioner should keep in mind that the rivastigmine plasma exposure associated with these sites was approximately 20-30% lower.

There was no relevant accumulation of rivastigmine or the metabolite NAP226-90 in plasma in patients with Alzheimer's disease, except that with patch treatment plasma levels on the second day were higher 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 1.8-2.7 l/kg.

Metabolism:

Rivastigmine is rapidly and extensively metabolised with an apparent elimination half-life in plasma of approximately 3.4 hours after patch removal. Elimination was absorption rate limited (flip-flop kinetics), which explains the longer $t_{1/2}$ 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 decarbamylated metabolite. 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 litres/h after a 0.2 mg intravenous dose and decreased to 70 litres/h after a 2.7 mg intravenous dose, which is consistent with the non-linear, overproportional 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 treatment. Less NAP226-90 is formed following patch application, presumably because of the lack of presystemic (hepatic first pass) metabolism.

Elimination:

Unchanged rivastigmine is found in trace amounts in the urine; renal excretion of the metabolites is the major route of elimination. Following administration of ¹⁴C-rivastigmine, renal elimination was rapid and essentially complete (>90 %) within 24 hours. Less than 1% of the administered dose is excreted in the faeces.

Special populations:

Elderly subjects

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

Subjects with hepatic impairment

No study was conducted with the Exelon 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 - 65 % lower in mild (n=7, Child-Pugh score 5-6) and moderate (n=3, Child-Pugh score 7-9) 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 Section 4.2 Dose and method of administration and Section 4.4 Special warnings and precautions for use).

Subjects with renal impairment

No study was conducted with the Exelon 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 4.2 Dose and method of administration).

5.3 Pre-clinical safety data

Acute toxicity

The estimated oral LD₅₀ values in mice were 5.6 mg base/kg (males) and 13.8 mg base/kg (females). The estimated oral LD₅₀ values in rats were 8.1 mg base/kg (males) and 13.8 mg base/kg (females).

Repeated dose toxicity

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.

Mutagenicity

Rivastigmine was not mutagenic in *in vitro* tests for gene mutations and primary DNA damage and chromosomal damage *in vivo*. In tests for chromosomal damage *in vitro*, a small increase in the number of cells carrying chromosomal aberrations occurred at very high concentrations. However, as there was no evidence of clastogenic activity in the more relevant *in vivo* micronucleus test assessing chromosomal damage test, it is most

likely that the *in vitro* findings were false positive observations. 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.

Carcinogenicity

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 patches.

Reproductive toxicity

Oral studies in pregnant rats and rabbits with dose levels up to 2.3 mg base/kg/day gave no indication of teratogenic potential on the part of rivastigmine. Similarly, there was no evidence of adverse effects of rivastigmine on fertility, reproductive performance or *in utero* or postnatal growth and development in rats at given dose levels up to 1.1 mg base/kg/day (see Section 4.4 Special warnings and precautions for use - Women of child-bearing potential, pregnancy, breast-feeding and fertility). Specific dermal studies in pregnant animals have not been conducted.

Local tolerance

Rivastigmine patches were not phototoxic and are 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 patches to induce mild erythema in patients. A mild eye/mucosal irritation potential of rivastigmine was identified in a rabbit study (see Section 4.2 Dose and method of administration - Important administration instructions).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Vitamin E

poly butylmethacrylate

methyl-methacrylate

acrylic copolymer

silicone oil (Ph. Eur.)

6.2 Incompatibilities

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

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

Keep the patch in the sachet until use.

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

6.5 Nature and contents of container

Pack sizes: 3 patches; 7 patches; 30 patches

Packaging: Sachet; either paper/polyester/Al/polyacrylonitrile with acrylic pressure sensitive adhesive and silicone pressure sensitive adhesive, backing film 15 cm square; or paper/polyethylene terephthalate/polyethylene/aluminium/polyamide.

*Not all presentations may be marketed.

6.6 Special precautions for disposal

Used patches should be folded, with the adhesive surfaces pressed together, and discarded safely and out of the reach and sight of children.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

16 August 2007

10 DATE OF REVISION OF THE TEXT

3 June 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections Sections 6.3, 6.4, 6.5	Updated to Summary of Product Characteristics (SPC) format with minor editorial changes as required. Added information to align with new format
6.5	Addition of alternative packaging material

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