

# New Zealand Data Sheet

## EXELON® Rivastigmine 5 and 10 cm<sup>2</sup> Transdermal Patch

### Qualitative and quantitative composition

Each patch of 5 cm<sup>2</sup> contains 9 mg rivastigmine base, *in vivo* release rate of 4.6 mg/24 hours.

Each patch of 10 cm<sup>2</sup> contains 18 mg rivastigmine base, *in vivo* release rate of 9.5 mg/24 hours.

### Excipients

Vitamin E, poly butylmethacrylate, methyl-methacrylate, acrylic copolymer, silicone oil (Ph. Eur.).

### 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 for each patch dose as follows:

- with “AMCX” for Exelon® Patch 5
- with “BHDI” for Exelon® Patch 10

### Indications

Treatment of patients with mild to moderately severe dementia of the Alzheimer type, also termed probable Alzheimer’s Disease or Alzheimer’s Disease.

### Dosage and administration

#### Dosage

Patches	Rivastigmine base dose load	Rivastigmine base <i>in vivo</i> release rates per 24 h
Exelon Patch 5	9 mg	4.6 mg
Exelon Patch 10	18 mg	9.5 mg

**Initial 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.

**Maintenance dose:** Exelon Patch 10 is the recommended maintenance daily dose which can be continued for as long as a therapeutic benefit for the patient exists.

- 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 several 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**

Rivastigmine 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 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.

The patch should be pressed down firmly until the edges stick well. It can be used in everyday situations, including bathing and during hot weather.

The patch should be replaced by a new one after 24 hours. Only one patch should be worn at a time (see Overdose). The patch should not be cut into pieces. Patients and caregivers should be instructed accordingly.

### **Special population**

(see section Warnings and precautions)

### **Renal impairment**

No dose adjustment is necessary for patients with renal impairment (see Pharmacokinetic properties).

### **Paediatric patients**

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

## Contraindications

The use of Exelon is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other ingredients of the formulation (see Excipients).

## Warnings and precautions

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 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 Adverse effects).

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.

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 Adverse effects).
- to patients with active gastric or duodenal ulcers or patients predisposed to these conditions because gastric acid secretions may be increased.
- 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.

## Special populations

- Patients with body weight below 50 kg may experience more adverse events and may be more likely to discontinue due to adverse events. Particular caution should be exercised in titrating these patients above the recommended maintenance dose of Exelon Patch 10.
- Hepatic impairment: 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 Pharmacokinetic properties).

## Interactions

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.

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,  $\beta$ -blockers, 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.

In view of its pharmacodynamic effects, rivastigmine should not be given concomitantly with other cholinomimetic drugs and might interfere with the activity of anticholinergic medications.

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

## **Pregnancy and breast-feeding**

### **Pregnancy**

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.

### **Breast-feeding**

It is not known if Exelon is excreted into human milk, and patients on Exelon should therefore not breast-feed.

## **Driving and using 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.

## **Adverse 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.

Table 1 displays the adverse drug reactions reported in 594 patients with Alzheimer’s dementia treated in a specific 24-week double-blind, placebo and active-controlled clinical study with Exelon patches at all doses (Exelon Patch 5 to Exelon Patch 20).

**Table 1**

Adverse reactions 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.

<b>Metabolism and nutrition disorders</b>	
Common	Anorexia, decreased appetite
<b>Psychiatric disorders</b>	
Common	Anxiety, depression, insomnia
Uncommon:	Agitation, delirium, hallucinations
<b>Nervous system disorders</b>	
Common:	Dizziness, headache
Uncommon:	Cerebrovascular accident, syncope, somnolence
<b>Cardiac disorders</b>	
Uncommon:	Cardiac arrhythmia (e.g. bradycardia, supraventricular extrasystole)
<b>Gastrointestinal disorders</b>	
Very common:	Vomiting, nausea
Common:	Diarrhoea, dyspepsia, abdominal pain
Uncommon:	Gastric ulcer, gastrointestinal haemorrhage (e.g. hemorrhagic duodenitis)
<b>Skin and subcutaneous tissue disorders</b>	
Uncommon:	Hyperhidrosis
<b>General disorders and administration site conditions</b>	
Common:	Application site reactions, application site erythema, application site pruritus, oedema, fatigue, asthenia
Uncommon:	Contact dermatitis, malaise
<b>Investigations</b>	
Common:	Weight decrease

### **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, fall, seizure. Worsening of Parkinson’s disease has been observed in patients with Parkinson’s disease who were treated with Exelon patches.

Frequency not known: dehydration, hepatitis, aggression, restlessness, and sick sinus syndrome.

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

Very rare: urinary infection, severe vomiting associated with oesophageal rupture.

Rare: angina pectoris, myocardial infarction, duodenal ulcers.

Uncommon: abnormal liver function tests.

Common: tremor, confusion.

### Information from clinical trials in patient with Alzheimer's dementia treated with Exelon patches

The following adverse events were reported in patient with Alzheimer's dementia treated with Exelon patches.

**Table 2** Adverse events ( $\geq 2\%$  in all Exelon Patch groups) from the specific 24-week clinical trial conducted with Exelon patches in patients with Alzheimer's dementia.

	Exelon Patch 10 group	Exelon Patch 20 group	Exelon capsules 12 mg/day	Placebo	All Exelon patches group
	n (%)	n (%)	n (%)	n (%)	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)

#### Skin irritation:

Skin irritation, when observed, was mostly slight or mild in severity and was rated as severe in  $\leq 2.2\%$  of Exelon Patch patients, versus  $\leq 1.0\%$  of placebo patch patients.

#### 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, hypertension and hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur.

Ingestion of 46 mg has occurred in one case; following conservative management the patient fully recovered within 24 hours.

Overdose with Exelon patches resulting from misuse/medication errors (application of multiple patches at a time) has been reported in the post-marketing setting. The typical symptoms reported among these cases are similar to those seen with cases of overdose associated with Exelon oral formulations.

## **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 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 sulfate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

## **Clinical Pharmacology**

### **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 in Alzheimer's Dementia

The efficacy of Exelon patches in patients with Alzheimer's dementia has been demonstrated in a 24-week double-blind core study and its open-label extension phase. Patients involved in this 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) and 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 3.

**Table 3 24-week results for the three assessment tools**

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

<sup>\*</sup>p<0.05 versus placebo

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

<sup>1</sup> 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.

<sup>2</sup> 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 4. 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 Results for clinically relevant responders from the 24-week study**

	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 <sup>*</sup>	20.2 <sup>**</sup>	19.0 <sup>**</sup>	10.5

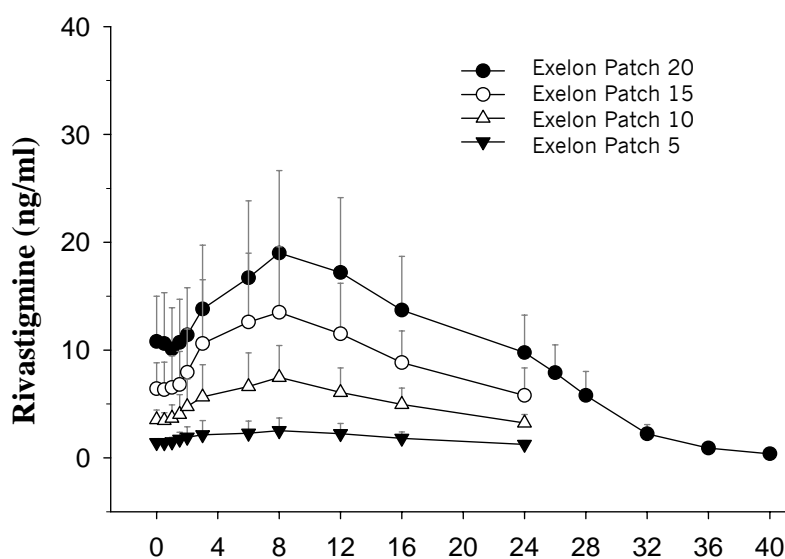
<sup>\*</sup>p<0.05, <sup>\*\*</sup>p<0.01 versus placebo

## Pharmacokinetics (PK)

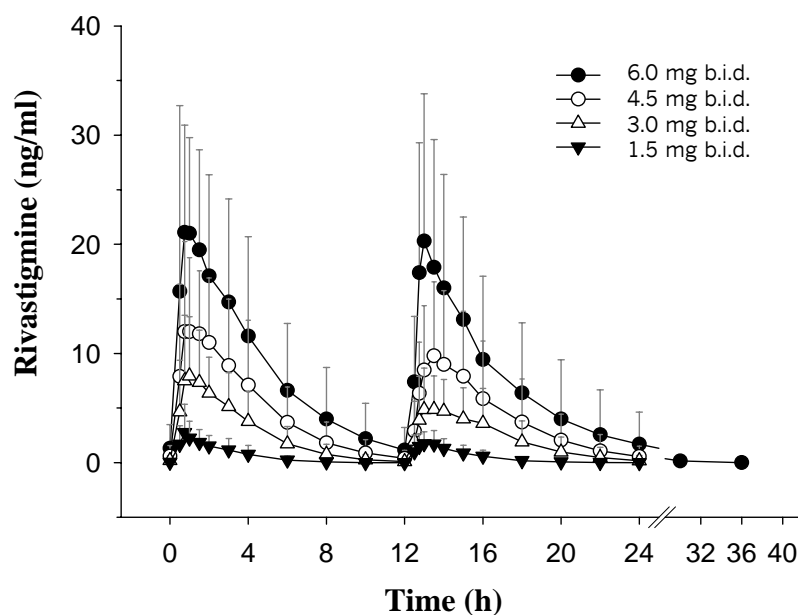
### Absorption

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 modeling the Exelon Patch 20 exhibited exposure (AUC<sub>24h</sub>) 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 Dosage and 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 ( $AUC_{\infty}$ ) 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 evidence from in vitro and 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  $AUC_{\infty}$  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  $^{14}C$ -rivastigmine, renal elimination was rapid and essentially complete (>90 %) within 24 hours. Less than 1% of the administered dose is excreted in the faeces.

### **Special population**

#### **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.

## **Subjects with renal impairment**

No study was conducted with the Exelon patches in subjects with renal impairment. After oral administration,  $C_{max}$  and AUC of rivastigmine were more than twice as high in Alzheimer patients with moderate renal impairment compared with healthy subjects; however there were no changes in  $C_{max}$  and AUC of rivastigmine in Alzheimer patients with severe renal impairment.

## **Non-clinical safety data**

### **Acute toxicity**

The estimated oral  $LD_{50}$  values in mice were 5.6 mg base/kg (males) and 13.8 mg base/kg (females). The estimated oral  $LD_{50}$  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.

### **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. Specific dermal studies in pregnant animals have not been conducted.

### **Dermal toxicity**

Rivastigmine patches were not phototoxic. 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.

### **Pharmaceutical information**

#### **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.

#### **Special precautions for storage**

Do not store above 25°C.

Keep the patch in the sachet until use.

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

#### **Instructions 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.

#### **Medicine classification**

Prescription Medicine

#### **Name and address**

Novartis New Zealand Limited  
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#### **Date of preparation**

23 November 2010  
(Ref: BPI 01 November 2010)