**Exelon® Patch**  
(Rivastigmine)

**NAME OF THE DRUG**

Rivastigmine base

**Structural Formula:**

- Chemical name: (S)-N-ethyl-N-methyl-3-[1-(dimethylamino)ethyl]-phenyl carbamate
- Molecular formula: C\textsubscript{14}H\textsubscript{22}N\textsubscript{2}O\textsubscript{2}
- Molecular weight: 250.34
- CAS number: 123441-03-2

**DESCRIPTION**

Exelon® Patch is a thin, matrix-type transdermal patch consisting of three layers, that contains rivastigmine.

Rivastigmine base is a viscous, clear colourless to yellow to very slightly brown liquid.

The outside of the backing layer is beige and labelled. Each patch dose of Exelon® Patch is labelled as follows:
- Exelon® Patch 5 with “AMCX”
- Exelon® Patch 10 with “BHDI”

- **Excipients:** Alpha-tocopherol, dimeticon 12500 (silicone oil), Durotak 387-2353, Bio PSA Q7-4302, acrylates copolymer, Hostaphan RN 23 (occlusive backing film) and Scotchpak 9744 (release liner).
PHARMACOLOGY

Pharmacodynamics
Pathological changes in 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, memory and other cognitive processes. Rivastigmine, a brain-selective, pseudo-irreversible inhibitor of the enzymes acetyl- and butyryl-cholinesterase, 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. In addition, there is some evidence that cholinesterase inhibition could slow the formation of amyloidogenic β-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 enzyme by forming a covalently bound complex that temporarily inactivates the enzyme. 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, inhibition of acetylcholinesterase in CSF by rivastigmine is dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of BuChE activity in the CSF of 18 patients with Alzheimer’s Disease was similar to that of AChE, with a change from baseline of more than 60% after 6 mg rivastigmine twice daily. The effect of rivastigmine on AChE and BuChE activity in CSF (a reduction from baseline of 33% and 45%, respectively) was sustained in 11 patients after administration of rivastigmine at a mean dose of 8.6 mg/day for 12 months. 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, the Computerised Neuropsychological Test Battery (CNTB), in 18 patients with Alzheimer’s Disease treated with daily doses of rivastigmine for a duration of at least 3 consecutive days. However, only BuChE inhibition in CSF was significantly and consistently correlated with improvements in speed-, attention- and memory-related subtests of the CNTB. The clinical significance of the inhibitory effect of rivastigmine on BuChE in patients with Alzheimer’s Disease is unknown.

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 0.5-1 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 to virtually zero between doses (see Figure 1). Although less pronounced than with the oral formulation, exposure to rivastigmine ($C_{\text{max}}$ and AUC) increased over-proportionally by a factor of 2.6 when escalating from Exelon Patch 5 to Exelon Patch 10. The fluctuation index (FI), a measure of the relative difference between peak and trough concentrations (($C_{\text{max}} - C_{\text{min}})/C_{\text{avg}}$), was 0.58 for Exelon Patch 5 and 0.77 for Exelon Patch 10, thus demonstrating a much smaller fluctuation between trough and peak concentrations than for the oral formulation (FI = 3.96 (6 mg/day) and 4.15 (12 mg/day)).

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

Figure 1: Rivastigmine plasma concentrations following dermal 24-hour patch application (top panel) or oral (twice daily) capsule (bottom panel)
bodyweight) was 43% (C$\text{max}$) and 49% (AUC$\text{0-24h}$) 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$\text{max}$) and 43% (AUC$\text{0-24h}$) 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 that special attention should be given to patients with very low body weight during up-titration. Rivastigmine was well released from the transdermal system over a 24-hour dermal application with approximately 50% of the drug load being 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. 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%). The apparent volume of distribution of rivastigmine is in the range of 1.8-2.7 L/kg. Rivastigmine distributes equally between blood and plasma with a blood-to-plasma partition ratio of 0.9 at concentrations ranging from 1-400 ng/mL.

**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, which explains the longer t$\text{\frac{1}{2}}$ 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.
Excretion:
Unchanged rivastigmine is not found 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.

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

Pharmacokinetics in renal impairment:
Following a single 3 mg dose, mean oral clearance of rivastigmine is 64% lower in moderately impaired renal patients ($n=8$, GFR 10-50 mL/min) than in healthy subjects ($n=10$, GFR 60 mL/min); $CL/F=1.7$ L/min (cv=45%) and 4.8 L/min (cv=80%), respectively. In severely impaired renal patients ($n=8$, GFR <10mL/min), mean oral clearance of rivastigmine is 43% higher than in healthy subjects ($n=10$, GFR 60 mL/min); $Cl/F = 6.9$ L/min and 4.8 L/min, respectively. For unexplained reasons, the severely impaired renal patients had a higher clearance of rivastigmine than moderately impaired patients. However, dosage adjustment may not be necessary in renally impaired patients as the dose of the drug is individually titrated to tolerability (see "DOSAGE AND ADMINISTRATION - Use in patients with renal or hepatic impairment").

Pharmacokinetics in hepatic impairment:
Following a single 3 mg dose, mean oral clearance of rivastigmine was 60% lower in hepatically impaired patients ($n=10$, biopsy proven) than in healthy subjects ($n=10$). After multiple 6 mg twice daily oral dosing, the mean clearance of rivastigmine was 65% lower in mild ($n=7$, Child-Pugh score 5-6) and moderate ($n=3$, Child-Pugh score 7-9) hepatically impaired patients (biopsy proven, liver cirrhosis) than in healthy subjects ($n=10$). Dosage adjustment is not necessary in hepatically impaired patients as the dose of drug is individually titrated to tolerability. (see "DOSAGE AND ADMINISTRATION - Use in patients with renal or hepatic impairment").

Special population:
Gender and race:
No specific pharmacokinetic study was conducted to investigate the effect of gender and race on the disposition of Exelon, but a population pharmacokinetic analysis indicates that gender ($n=277$ males and 348 females) and race ($n=575$ white, 34 black, 4 asian and 12 other) did not affect the clearance of Exelon.

Nicotine use:
Population pharmacokinetic analysis showed that nicotine use increases the oral clearance of rivastigmine by 23% ($n=75$ smokers and 549 non-smokers).
CLINICAL TRIALS

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 1. Patch 5 was intended as the initiating dose for patients not currently being treated with oral formulations. No specific 24-week results for the three assessment tools were collected during the study and its extension phase for Patch 5.

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Table 1: 24-week results for the three independent, domain-specific assessment tools (ADAS-Cog, ADCS-CGIC and ADCS-ADL).

<table>
<thead>
<tr>
<th>ITT-LOCF population</th>
<th>Exelon Patch 10</th>
<th>Exelon capsule 12 mg/day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>(n=248)</td>
<td>(n=253)</td>
<td>(n=281)</td>
</tr>
<tr>
<td>Mean change at week 24 ± SD</td>
<td>27.0 ±10.3</td>
<td>27.9 ± 9.4</td>
<td>28.6 ± 9.9</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>-0.6 ± 6.4</td>
<td>-0.6 ± 6.2</td>
<td>1.0 ± 6.8</td>
</tr>
<tr>
<td></td>
<td>0.005*1</td>
<td>0.003*1</td>
<td></td>
</tr>
<tr>
<td>ADCS-CGIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score ± SD</td>
<td>(n=248)</td>
<td>(n=253)</td>
<td>(n=278)</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>3.9 ± 1.20</td>
<td>3.9 ± 1.25</td>
<td>4.2 ± 1.26</td>
</tr>
<tr>
<td></td>
<td>0.010*2</td>
<td>0.009*2</td>
<td></td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>(n=247)</td>
<td>(n=254)</td>
<td>(n=281)</td>
</tr>
<tr>
<td>Mean change at week 24 ± SD</td>
<td>50.1 ± 16.3</td>
<td>49.3 ± 15.8</td>
<td>49.2 ± 16.0</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>-0.1 ± 9.1</td>
<td>-0.5 ± 9.5</td>
<td>-2.3 ± 9.4</td>
</tr>
<tr>
<td></td>
<td>0.013*1</td>
<td>0.039*1</td>
<td></td>
</tr>
</tbody>
</table>

* 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 2. 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 2: Results for clinically relevant responders from the 24-week study

<table>
<thead>
<tr>
<th>Patients with Clinically Significant Response (%)</th>
<th>Exelon Patch 10</th>
<th>Exelon capsule 12mg/day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL</td>
<td>17.4*</td>
<td>19.0**</td>
<td>10.5</td>
</tr>
</tbody>
</table>

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

Effects on the ADAS-Cog

Figure 2 illustrates the time course for the change from baseline in ADAS-Cog scores by treatment group over the 24-week study. At 24 weeks, the mean differences in the ADAS-Cog change scores for the Exelon-treated patients, compared to the patients on placebo, was 1.6 units for the Exelon Patch 9.5 mg/24 hours and Exelon capsule 6 mg BID groups. The difference between each of these groups and placebo was statistically significant.

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

Effects on the ADCS-CGIC

Figure 3 is a histogram of the distribution of patients’ scores on the ADCS-CGIC for all 3 treatment groups. At 24 weeks, the mean difference in the ADCS-CGIC scores for the comparison of patients in each of the Exelon-treated groups with the patients on placebo, was 0.3 units. The difference between each of these groups and placebo was statistically significant.
**INDICATIONS**

Exelon is indicated for the treatment of patients with mild to moderately severe dementia of the Alzheimer’s type.

**CONTRAINDICATIONS**

The use of Exelon is contraindicated in patients with known hypersensitivity to rivastigmine, to other components of the formulation, or to other carbamate derivatives.

Exelon is contraindicated in patients with severe liver impairment since it has not been studied in this population.

**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 (see "DOSAGE and ADMINISTRATION").
Gastrointestinal Adverse reactions:
Caregivers should be advised that nausea and vomiting are associated with the use of the drug along with possible anorexia and weight loss.

Nausea and Vomiting
Gastrointestinal disorders such as nausea and vomiting 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 (see “ADVERSE REACTIONS”).

In the controlled clinical trial, 7% of patients treated with the Exelon Patch 9.5mg/24 hours developed nausea, as compared to 23% of patients who received the Exelon capsule at doses up to 6 mg BID and 5% of those who received placebo. In the same clinical trial, 6% of patients treated with Exelon Patch 9.5mg/24 hours developed vomiting, as compared with 17% of patients who received the Exelon capsule at doses up to 6 mg BID and 3% of those who received placebo. The proportion of patients who discontinued treatment due to vomiting was 0% of the patients who received the Exelon Patch 9.5mg/24 hours as well as 2% of patients who received the Exelon capsule at doses up to 6 mg BID and 0% of those who received placebo. Vomiting was severe in 0% of patients who received the Exelon Patch 9.5mg/24 hours and 1% of patients who received the Exelon capsule at doses up to 6 mg BID and 0% of those who received placebo.

Anorexia
Patients with Alzheimer’s disease may lose weight whilst taking cholinesterase inhibitors, including rivastigmine.

In the controlled clinical trial, 3% of the patients treated with the Exelon Patch 9.5 mg/24 hours were recorded as developing decreased appetite or anorexia, as compared with 9% of patients who received the Exelon capsule at doses up to 6 mg BID and 2% of those who received placebo.

Diarrhea
In the controlled clinical trial, 6% of the patients treated with the Exelon Patch 9.5 mg/24 hours developed diarrhea, as compared with 5% of patients who received the Exelon capsule at doses up to 6 mg BID and 3% of those who received placebo.

Weight Loss
The patient’s weight should be monitored during therapy with Exelon patches.

In the controlled clinical trial, the proportion of patients who had weight loss equal to or greater than 7% of their baseline weight was 8% of those treated with the Exelon Patch 9.5 mg/24 hours, 11% of patients who received the Exelon capsule at doses up to 6 mg BID and 6% of those who received placebo.

It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.

Anaesthesia:
Exelon, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type relaxation during anaesthesia.
Use in patients with cardiovascular conditions:
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 REACTIONS”). Drugs that increase cholinergic activity may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, Exelon was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities.

Use in patients with active gastric or duodenal ulcers or patients predisposed to these conditions:
Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g. those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). Clinical studies of Exelon have shown no significant increase relative to placebo in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Use in patients predisposed to urinary obstruction:
Cholinomimetics may exacerbate urinary obstruction. Although this has not been observed with Exelon, caution is recommended in such cases.

Use in patients predisposed to seizures:
Cholinomimetics may exacerbate seizures. However, seizure activity also may be a manifestation of Alzheimer's Disease. Although this has not been observed with Exelon, caution is recommended in such cases.

Use in patients with pulmonary conditions:
As with other cholinomimetics, Exelon should be used with caution in patients with a history of asthma or obstructive pulmonary disease. There is evidence from animal studies that rivastigmine may potentiate bronchoconstriction.

Use in patients with low body weight:
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 that special attention should be given to patients with very low body weight during up-titration.
Use in children:
There is no experience with the use of Exelon in children. Exelon is not recommended for use in children.

Use in pregnancy (Pregnancy Category B2)
Oral rivastigmine was not teratogenic in rats and rabbits at doses producing maternal toxicity, but systemic drug exposures in these studies were below the maximum therapeutic value. No specific dermal studies have been performed. The safety of Exelon transdermal patches in human pregnancy has not been established.

Use in lactation
Rivastigmine and its metabolites are excreted into the milk of lactating rats and rabbits. It is not known whether excretion into human milk occurs, and patients taking Exelon transdermal patches should not breast-feed.

Use in patients with renal impairment:
No study was conducted with the Exelon transdermal patches in subjects with renal impairment. However, due to increased exposure in renal impairment dosing recommendations to titrate according to individual tolerability should be closely followed (see “PHARMACOLOGY - Pharmacokinetics in renal impairment”).

Use in patients with hepatic impairment:
No study was conducted with the Exelon transdermal patches in subjects with hepatic impairment. However, patients with clinically significant hepatic impairment might experience more adverse events. (see “PHARMACOLOGY - Pharmacokinetics in hepatic impairment”).

Effects on ability to drive or operate machinery:
Alzheimer’s disease may cause gradual impairment of driving performance or compromise the ability to use machinery and rivastigmine may induce dizziness and somnolence, mainly when initiating treatment or increasing the dose. Therefore, the ability of Alzheimer’s patients to continue driving or operating complex machines should be routinely evaluated by the treating physician.

Effects on fertility:
Oral rivastigmine, at doses which achieved systemic drug exposures below the therapeutic value, had no effect on fertility in rats. Specific dermal studies have not been conducted. The effects of rivastigmine on human fertility are not known.

Genotoxicity:
Rivastigmine was not genotoxic in tests for gene mutation in bacteria and primary DNA damage in mammalian cells in vitro. In tests for chromosomal damage in vitro, a small increase in the number of cells carrying chromosomal aberrations occurred at very high concentrations. However, there was no evidence of clastogenicity in the more relevant in vivo test in mice.
**Carcinogenicity:**
No evidence of carcinogenicity was found in oral and topical studies in mice, or in an oral study in rats, at the maximum tolerated dose of rivastigmine. However, achieved systemic exposures to rivastigmine and the phenolic metabolite NAP226-90 in animals were lower than in humans treated with Exelon transdermal patches at the maximum recommended dose.

**Dermal toxicity:**
There was no evidence of phototoxicity in guinea pigs exposed to UV-A radiation following a 30-minute application of a rivastigmine patch.

**Interactions with other medicines**
The patient group to be treated frequently takes additional medications. Therefore, physicians should carefully evaluate any concomitant drug administration in this patient group.

Exelon transdermal patches should not be used with any other acetylcholinesterase inhibitors.

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

No pharmacokinetic interaction was observed between Exelon and digoxin, warfarin, diazepam or fluoxetine in single-dose studies in healthy volunteers. The elevation of prothrombin time induced by warfarin was not affected by administration of Exelon. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and Exelon.

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

Population pharmacokinetic analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antidiabetics (n=21), antihypertensives (n=72), beta-blockers (n=42), calcium channel blockers (n=75), antianginals (n=35), non-steroidal anti-inflammatory drugs (n=79), oestrogens (n=70), salicylate analgesics (n=177) and antihistamines (n=15). In addition, in clinical trials, no increased risk of clinically relevant untoward effects was observed in patients treated concomitantly with Exelon and these agents.

In view of its pharmacodynamic effects, Exelon should not be given concomitantly with other cholinomimetic drugs. Exelon may also interfere with the activity of anticholinergic medications.
A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

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

**ADVERSE REACTIONS**

In general, adverse events are mild to moderate and usually resolve without therapeutic intervention. Incidence and severity of adverse events generally increase with higher doses.

**Adverse Events Reported in Controlled Trials**

Table 1 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Exelon transdermal patches than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.
**Table 3** Adverse events (≥2% in all Exelon Patch 10 group) from the specific 24-week clinical trial conducted with Exelon patches in patients with Alzheimer’s dementia.

<table>
<thead>
<tr>
<th>Adverse events in patients with dementia associated with Alzheimer’s disease (≥2% in all Exelon Patch groups)</th>
<th>Exelon Patch 10 n (%)</th>
<th>Exelon capsules 12 mg/day n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients studied</td>
<td>291</td>
<td>294</td>
<td>302</td>
</tr>
<tr>
<td>Total patients with AE(s)</td>
<td>147 (50.5)</td>
<td>186 (63.3)</td>
<td>139 (46.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>21 (7.2)</td>
<td>68 (23.1)</td>
<td>15 (5.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (6.2)</td>
<td>50 (17.0)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>18 (6.2)</td>
<td>16 (5.4)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>8 (2.7)</td>
<td>16 (5.4)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (2.4)</td>
<td>22 (7.5)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2 (0.7)</td>
<td>12 (4.1)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (3.4)</td>
<td>18 (6.1)</td>
<td>5 (1.7)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>7 (2.4)</td>
<td>14 (4.8)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Depression</td>
<td>11 (3.8)</td>
<td>13 (4.4)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4 (1.4)</td>
<td>6 (2.0)</td>
<td>6 (2.0)</td>
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<tr>
<td>Abdominal pain</td>
<td>7 (2.4)</td>
<td>4 (1.4)</td>
<td>2 (0.7)</td>
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<td>Asthenia</td>
<td>5 (1.7)</td>
<td>17 (5.8)</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9 (3.1)</td>
<td>5 (1.7)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (1.7)</td>
<td>2 (0.7)</td>
<td>4 (1.3)</td>
</tr>
</tbody>
</table>

In this clinical trial, Patch 5 was intended as the initiating dose for patients not currently being treated with oral formulations. Adverse events were collected per target dose group. It is expected that some of the adverse events reported in Table 3 may occur with Patch 5.

**Skin irritation:** In clinical trials, skin reactions were measured at each visit using a skin irritation rating scale that rated the degree of erythema, oedema, scaling, fissures, pruritus and pain/stinging/burning at the application site. The most commonly observed symptom was erythema which disappeared within 24 hours in the vast majority of patients. In a 24-week double-blind study, the most commonly observed symptoms (skin irritation rating scale) with Exelon Patch 10 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 Patch 10 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 9.5 mg/24 h transdermal patch group.

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.

**Adverse Drug Reactions Reported in Controlled Trials**

The overall incidence of adverse events (AEs) in patients treated with Exelon Patch 10 was lower than the rate in patients who received 3 to 12 mg/day Exelon capsule treatment (50.5% with Exelon Patch 10 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 Patch 10 group compared to the rivastigmine 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).

Table 4: Adverse drug reactions (events reasonably believed to be causally related to the medicinal product) reported in 291 patients with Alzheimer’s dementia treated in a specific 24-week double-blind, placebo and active-controlled clinical study with Exelon patches at target dose 9.5mg/24h (4.6mg/24h titrated to 9.5mg/24h).

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection and infestation</td>
<td>Common: Urinary tract infection</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common: Anorexia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common: Anxiety, depression, delirium</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common: Headache, syncope. Very rare: Extrapyramidal symptoms</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon: Bradycardia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common: Vomiting, nausea, diarrhoea, dyspepsia, abdominal pain. Uncommon: Gastric ulcer</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common: Rash</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common: Application site skin reactions (e.g. application site erythema, application site pruritus, application site oedema, application site dermatitis, application site irritation), asthenic conditions (e.g. fatigue, asthenia), pyrexia, weight decreased</td>
</tr>
</tbody>
</table>

The following adverse drug reactions have only been observed with rivastigmine capsules and oral solution and not in clinical studies with Exelon Patch 10: Dizziness, loss of appetite (very common); agitation, somnolence, malaise, tremor, confusion, sweating increased (common); insomnia, accidental fall, abnormal hepatic function tests (uncommon); seizures, duodenal ulcers, angina pectoris (rare); cardiac arrhythmia (e.g. atrio-ventricular block, atrial fibrillation and tachycardia), hypertension, mild pancreatitis, gastrointestinal hemorrhage, hallucination and some cases of severe vomiting were associated with esophageal rupture (very rare).
DOSAGE AND 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. The patch should not be used with any other acetylcholinesterase inhibitors (see “PRECAUTION – Interaction with other drugs”). Patients and caregivers should be instructed accordingly.

Starting 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 interruption:
Treatment should be temporarily interrupted if gastrointestinal adverse effects 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. If adverse effects persist, the dose should be temporarily reduced to the previous well-tolerated dose.

Re-initiation of therapy:
If treatment is interrupted for longer than several days, treatment should be re-initiated with Exelon Patch 5 (see "PRECAUTIONS").

Switching from capsules or oral solution:
Based on comparative exposure between oral and transdermal rivastigmine, patients treated with Exelon capsules or Exelon oral solution can be switched directly to Exelon transdermal patches:

- A patient on a total daily oral rivastigmine dose of 3mg can be switched to Exelon Patch 5.
- A patient on a total daily oral rivastigmine dose of 6mg can be switched to Exelon Patch 5.
- A patient on a stable and well tolerated total daily oral rivastigmine dose of 9mg can be switched to Exelon Patch 10. If the daily oral dose of 9 mg has not been stable and well tolerated, a switch to Exelon Patch 5 is recommended.
- A patient on a total daily oral rivastigmine dose of 12mg can be switched to Exelon Patch 10.

After switching to Exelon Patch 5, provided these are well tolerated after a minimum of four weeks of treatment and if well tolerated, the dose of Exelon Patch 5 should be increased to Exelon Patch 10, which is the recommended effective dose.

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

**Use in patients with renal or hepatic impairment:**

Due to anticipated increased exposure in renal impairment and mild to moderate hepatic impairment, dosing recommendations to titrate according to individual tolerability should be closely followed (see "PHARMACOLOGY - Pharmacokinetics in renal impairment; Pharmacokinetics in hepatic impairment").

**Use in patients with low body weight:**

The effect of bodyweight on drug exposure suggests that special attention should be given to patients with very low body weight during up-titration (see “PRECAUTIONS – Use in patients with low body weight”).

**OVERDOSAGE**

**Symptoms:**

Most cases of accidental overdose have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued Exelon treatment. Where symptoms have occurred, they have included severe nausea, vomiting, diarrhoea, hypertension, hallucinations, salivation, sweating, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when co-administered with quaternary anticholinergics such as glycopyrrolate. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. There are currently no data in overdose with Exelon patches. However, ingestion of 46 mg of rivastigmine occurred in one case; following conservative management, the patient fully recovered within 24 hours.

**Treatment:**

As rivastigmine has a plasma half-life of about 1 hour and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that, in cases of asymptomatic overdoses, no further dose of Exelon should be administered 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.

Due to the short half-life of Exelon, dialysis (haemodialysis, peritoneal dialysis or haemofiltration) would not be clinically indicated in the event of an overdose.
In massive overdoses, atropine can be used. An initial intravenous dose of 0.03 mg/kg atropine sulphate is recommended, with subsequent doses based upon clinical response. Use of hyoscine as an antidote is not recommended.

**PRESENTATION AND STORAGE**

**Presentation:**
Two strengths of Exelon patches are available, providing the following in vivo release rates.

<table>
<thead>
<tr>
<th>Patches</th>
<th>Surface area cm²</th>
<th>Rivastigmine base dose load</th>
<th>Rivastigmine base in vivo release rates per 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exelon Patch 5</td>
<td>5</td>
<td>9 mg</td>
<td>4.6 mg</td>
</tr>
<tr>
<td>Exelon Patch 10</td>
<td>10</td>
<td>18 mg</td>
<td>9.5 mg</td>
</tr>
</tbody>
</table>

The Exelon patches are individually sealed in child-resistant sachets made of a paper/polyester/aluminium/polyacrylonitrile multilaminated material. The sachets are packed into cartons of 30 patches.

**Storage:**
Store below 25°C. Keep the patch in the sachet until use. Do not freeze. Keep out of the reach of children.

**Special precaution 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.

**POISON SCHEDULE**

**Poisons schedule:** S4

**SPONSOR**

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