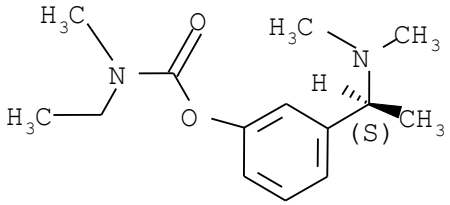
EXELON® PATCH

(rivastigmine)

NAME OF THE MEDICINE

Rivastigmine base

Structural Formula:



Chemical name:	3-[(1S)-1-(Dimethylamino)ethyl]phenyl ethyl(methyl)carbamate
Molecular formula:	$C_{14}H_{22}N_2O_2$
Molecular weight:	250.34
CAS number:	123441-03-2

DESCRIPTION

Exelon Patch is a thin, matrix-type transdermal patch consisting of three layers, one of which contains rivastigmine. Exelon Patches are available in three strengths:

Exelon® Patch 5: Each patch of 5 cm^2 contains 9 mg rivastigmine.

Exelon® Patch 10: Each patch of 10 cm^2 contains 18 mg rivastigmine.

Exelon® Patch 15: Each patch of 15 cm^2 contains 27 mg 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 strength is labelled as follows:

- Exelon® Patch 5 with “AMCX” and "Exelon® Patch 5 (rivastigmine)”

- Exelon® Patch 10 with “BHDI” and "Exelon® Patch 10 (rivastigmine)”

- Exelon® Patch 15 with “CNFU” and “Exelon® Patch 15 (rivastigmine)”

Excipients: Alpha tocopherol, dimeticone 12500, Durotak 387-2353(ARPING No: 2261), Bio-PSA 7-4302 Silicone Adhesive (ARPING No: 12567), and acrylates copolymer.

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 ß-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).

As with Exelon Patch 5 and 10, rivastigmine plasma concentrations following Exelon Patch 15 increased slowly, reaching T_{max} at approximately 8 h post-application (see Figure 1). The mean (SD) C_{max} following administration of Exelon Patch 15 at steady-state in AD patients (Study D2331) was 14.1 (6.3) ng/mL compared to 2.7 (1.2) ng/mL and 7.9 (2.9) ng/mL for Exelon Patches 5 and 10, respectively (see Table 1); whereas mean (SD) AUC_{24h} was 233 (83.2) ng.h/mL compared to 46.3 (17.2) and 127 (41.4) ng h/mL, respectively (Table 1).

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_{max} and AUC) increased over-proportionally by a factor of 2.6 when escalating from Exelon Patch 5 to Exelon Patch 10 and by a factor of 4.9 when escalating from Exelon Patch 5 to Patch 15. Results from Study 2331 showed the fluctuation index (FI), a measure of the relative difference between peak and trough concentrations ((C_{max}-C_{min})/C_{avg}), was 0.58 for Exelon Patch 5, 0.77 for Exelon Patch 10, and 0.72 for Exelon Patch 15, 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)).

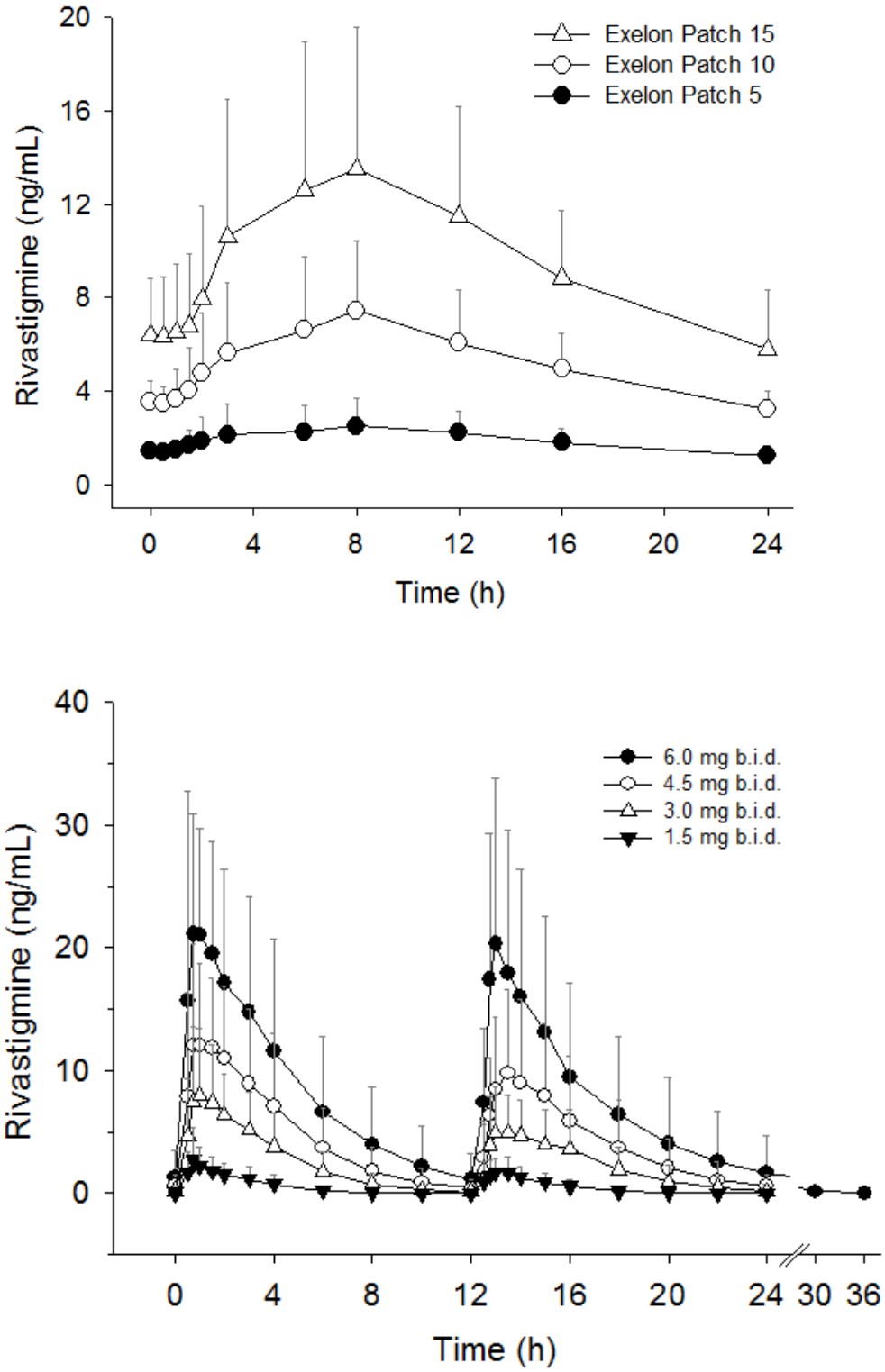
Table 1: Comparative rivastigmine exposure parameters following multiple (qd) Exelon Patch 5, 10 and 15 applications [Study 2331]

	Rivastigmine Patch		
	C_{max} (ng/mL	AUC_{0-24} (h.ng/mL)	Fluctuation index
5cm² (9mg loaded, n = 22)			
Mean ± SD	2.71 ± 1.23	46.3 ± 17.2	0.58 ± 0.40
CV%	45.2	43.2	69.2
Median	2.57	47.6	0.61
Min-max	1.19-5.39	20.0-81.4	0.00-1.17
Geo. mean	2.45	43.2	
CV% Geo. mean	49.7	40.7	
10cm² (18mg loaded, n = 22)			
Mean ± SD	7.88 ± 2.88	127 ± 41.4	0.77 ± 0.32
CV%	36.6	32.6	42.2
Median	7.79	129	0.76
Min-max	2.76-12.9	41.4-198	0.15-1.26
Geo. mean	7.32	120	069
CV% Geo. mean	43.1	38.1	57.4
15cm² (27mg loaded, n = 19)			
Mean ± SD	14.1 ± 6.30	233 ± 83.2	0.72 ± 0.36
CV%	44.6	35.7	50.5
Median	15.3	255	0.61
Min-max	4.32-25.7	93.3-345	0.08-1.30
Geo. mean	12.6	217	0.60
CV% Geo. mean	55.4	42.9	81.3

The release rate of rivastigmine from Exelon Patch 15 is 13.3 mg/24 h as determined in AD patients at steady state (Study D2331) compared to 4.6 and 9.5 mg/24 h for Exelon Patch 5 and 10, respectively.

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)**



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 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_{∞}) 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 $t_{½}$ after patch (3.4 h) versus oral or i.v. administrations (1.4 to 1.7 h). Metabolism is primarily via cholinesterase-mediated hydrolysis to the 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, over proportional pharmacokinetics of rivastigmine due to saturation of its elimination.

The metabolite-to-parent AUC_{∞} ratio was around 0.7 after patch versus 3.5 after oral administration, indicating that much less metabolism occurred after dermal 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.

<u>Pharmacokinetics in the elderly:</u>

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

Mild to moderate Alzheimer's dementia

Study 2320 – 24 week placebo controlled study

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 2. 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.

Table 2: 24-week results for the three independent, domain-specific assessment tools (ADAS-Cog, ADCS-CGIC and ADCS-ADL).

	Exelon Patch 10	**Exelon** capsule 12 mg/day	**Placebo**
ITT-LOCF population	N = 251	N = 256	N = 282
ADAS-Cog			
	(n=248)	(n=253)	(n=281)
Mean baseline ± SD	27.0 ±10.3	27.9 ± 9.4	28.6 ± 9.9
Mean change at week 24 ± SD	-0.6 ± 6.4	-0.6 ± 6.2	1.0 ± 6.8
p-value versus placebo	0.005*[1]	0.003*[1]	
ADCS-CGIC			
	(n=248)	(n=253)	(n=278)
Mean score ± SD	3.9 ± 1.20	3.9 ± 1.25	4.2 ± 1.26
p-value versus placebo	0.010*[2]	0.009*[2]	
ADCS-ADL			
	(n=247)	(n=254)	(n=281)
Mean baseline ± SD	50.1 ± 16.3	49.3 ± 15.8	49.2 ± 16.0
Mean change at week 24 ± SD	-0.1 ± 9.1	-0.5 ± 9.5	-2.3 ± 9.4
p-value versus placebo	0.013*[1]	0.039*[1]	

* p≤0.05 versus placebo

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

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

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

The results for clinically relevant responders from the 24-week study are provided in Table 3. 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 3: Results for clinically relevant responders from the 24-week study

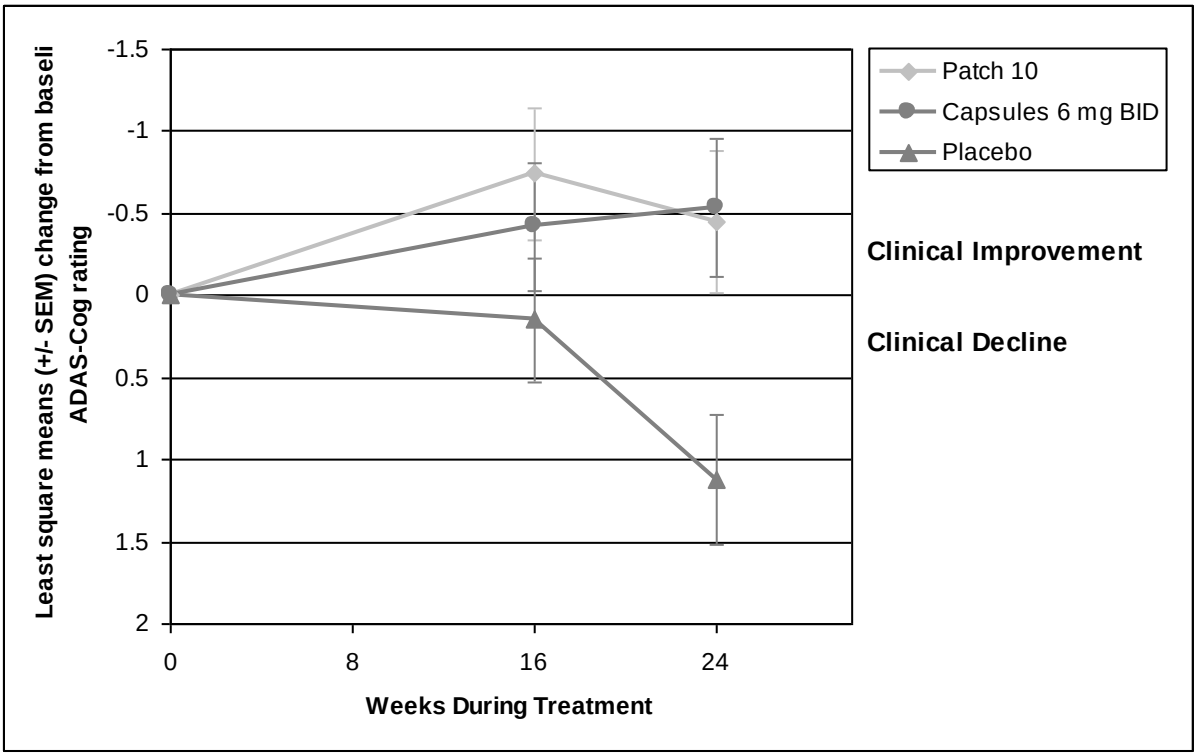
	Patients with Clinically Significant Response (%)		
	Exelon Patch 10	Exelon capsule 12mg/day	Placebo
At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL	17.4*	19.0**	10.5

*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.

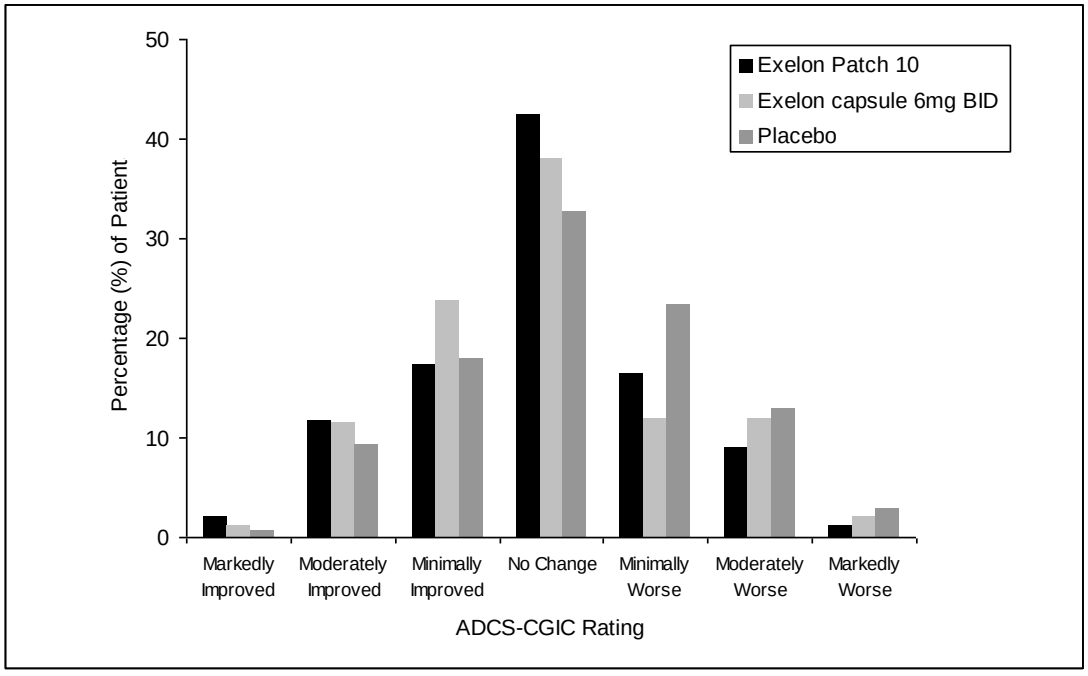
Figure 2: Time Course of the Change from Baseline in ADAS-Cog Score for Patients Observed at Each Time Point



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.

Figure 3: Distribution of ADCS-CGIC Scores for Patients Completing the Study



Moderate to severe Alzheimer's dementia

Study 2340

This study was a randomized double-blind clinical investigation in patients with Alzheimer's disease Mini-Mental State Examination (MMSE) score ≥ 10 and ≤ 24. The mean age of patients participating in this trial was 76 years with a range of 53-87 years. Approximately 65% of patients were women and 35% were men. The racial distribution was approximately Caucasian 97%, Black 2%, Asian 0.5%, and other races 1%. Approximately 27% of the patients were taking memantine throughout the entire duration of the study. Alzheimer's disease patients who received 24 to 48 weeks open label treatment with Exelon Patch 10cm^2 and who demonstrated functional and cognitive decline were randomized into treatment with either Exelon Patch 10cm^2 or Exelon Patch 15cm^2 in a 48-week double blind treatment phase.

The ability of the Exelon Patch 15cm^2 to improve overall function versus that provided by Exelon Patch 10cm^2 was assessed by the instrumental sub-scale of the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-IADL). The ADCS-IADL sub-scale is composed of items 7 to 23 of the caregiver-based ADCS-ADL scale. The ADCS-IADL assesses activities such as those necessary for communicating and interacting with other people, maintaining a household, and conducting hobbies and interests. A sum score is calculated by adding the scores of the individual items and can range from 0 to 56, with higher scores indicating less impairment.

The ability of the Exelon Patch 15cm^2 to improve cognitive performance over that provided by the Exelon Patch 10cm^2 was assessed by the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog).

Study 2340 was designed to compare the efficacy of Exelon Patch 10cm^2 versus that of Exelon Patch 15cm^2 during the 48-week double blind treatment phase as assessed by the co-primary outcome variables of the Alzheimer's Disease Cooperative Study- Instrumental Activities of Daily Living (ADCS-Instrumental ADL) at 48 weeks and the Alzheimer's disease assessment scale-cognitive (ADAS-cog) subscale at 48 weeks. The statistical analysis required showing significant superiority for the 15cm^2 patch over the 10cm^2 patch in both these endpoints to demonstrate efficacy.

Out of a total of 1584 patients enrolled in the initial open-label phase of the study, 567 patients showed functional and cognitive decline and were randomized into the 48-week double-blind treatment phase of the study. 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.The percentage of patients with decline was lower than expected, and the planned sample size (432 patients in each group during the DB phase) was not met. Two hundred eighty-seven (287) patients entered the 10cm^2 Exelon Patch treatment group and 280 patients entered the 15cm^2 Exelon Patch treatment group.

The study failed to show efficacy in that in one of two co-primary endpoints at week 48 – the difference between the treatment groups at Week 48 was statistically significant for the ADCS-Instrumental ADL score, but it was not for the ADAS-Cog scores.

Figure 4 illustrates the time course for the mean change from double-blind baseline in ADCS-IADL scores for each treatment group over the course of the 48-week treatment phase of the study.

Decline in the mean ADCS Instrumental ADL score from the double-blind baseline for the Intent to Treat–Last Observation Carried Forward (ITT-LOCF) analysis showed the 15cm^2 dose was statistically significantly superior to the 10cm^2 dose at weeks 16, 24, 32 and 48 (primary endpoint).

Figure 5 illustrates the time course for the mean change from double-blind baseline in ADAS-Cog scores for both treatment groups over the 48-week treatment phase. The between-treatment group difference for Exelon Patch 15cm^2 versus Exelon Patch 10cm^2 was nominally statistically significant at week 24 ($p = 0.027$), but not at week 48 ($p = 0.227$), which was the primary endpoint, nor any other time point.

Figure 4: Change from Baseline in ADCS-IADL total Score (Study 2340-ITT-DB-LOCF)

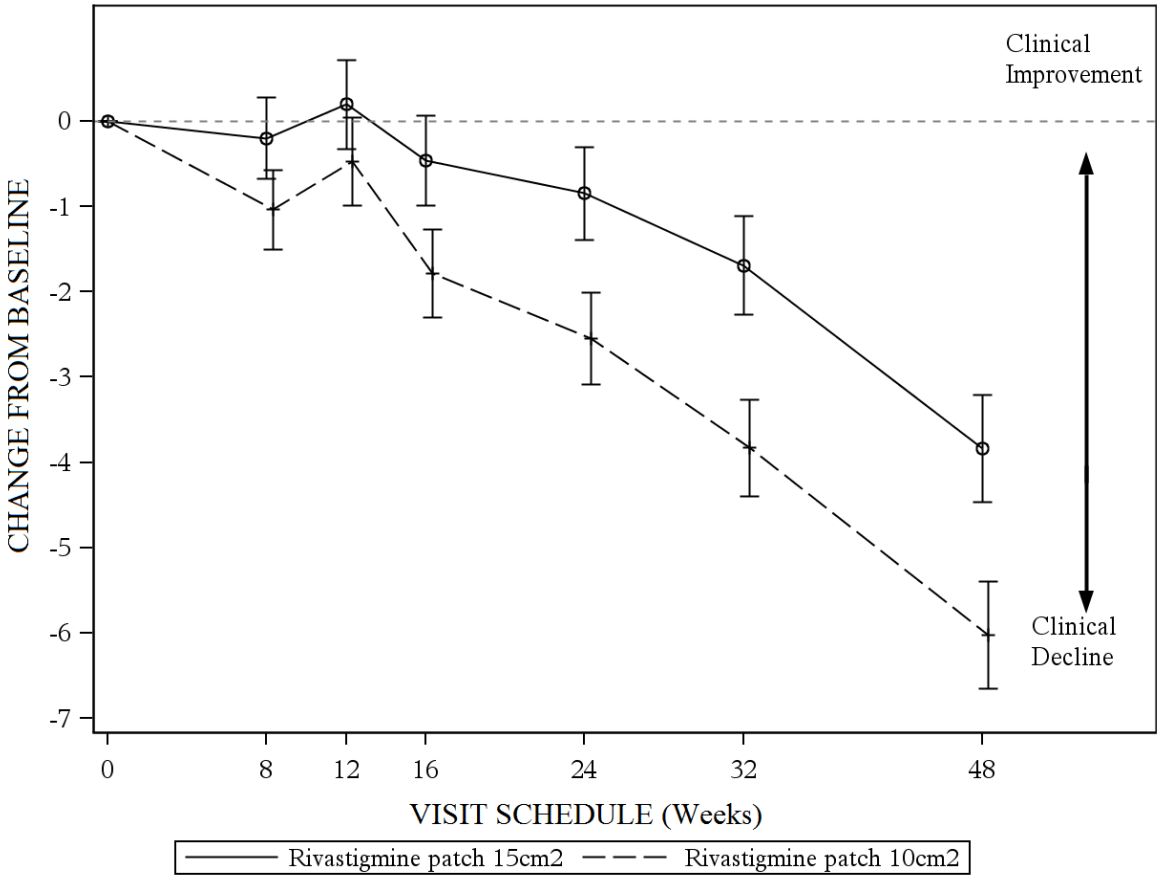
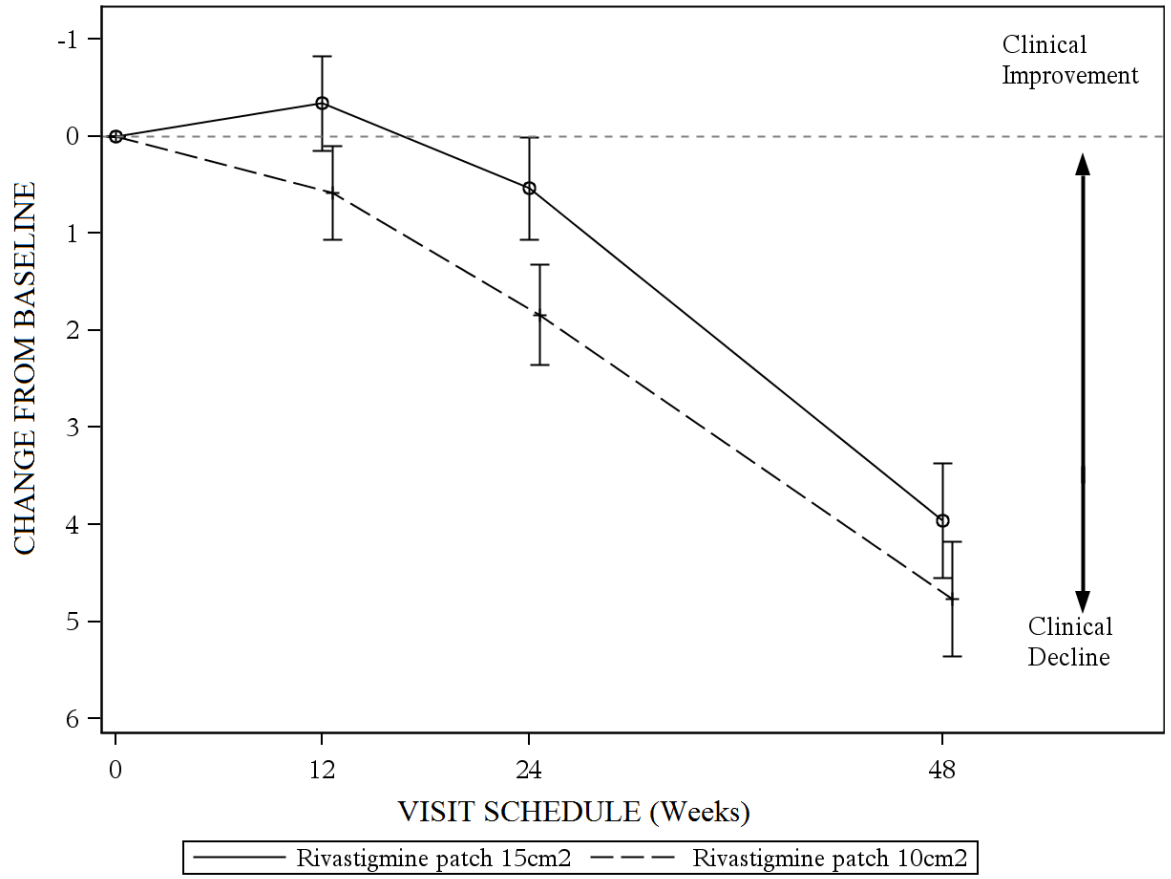


Figure 5: Change from Baseline in ADAS-Cog total Score (Study 2340–ITT-DB-LOCF)



Secondary Efficacy Measures

In the DB phase, functional decline was defined by either at least 1 point decrease in the ADCS-Instrumental ADL score in a visit and confirmed by the following visit/assessment or at least 2 points decrease from DB randomization baseline, and was still at least 1 point less at the subsequent confirmation visit. For time to functional decline in ADCS-Instrumental ADL in the DB phase the p-value of the log-rank test for treatment comparison was not significant (p = 0.186)

For Trail Making Test (Parts A and B) in the DB phase the between treatment group LSM differences were not statistically significant for the LOCF (week 48 part A p = 0.473; Part B p = 0.881).

In both the NPI-10 and NPI-D scales, the between dose treatment group differences were not statistically significant.

Subgroup analysis of moderate to severe Alzheimer's dementia patients in Study 2340

A *post-hoc* subgroup analysis of moderate to severe Alzheimer's dementia patients initial baseline MMSE score of 0 – 20 was undertaken. Although the subset population was quite large (91% of the original study patients), efficacy post-hoc analyses of Study D2340 moderate-to-severe subjects were not formally powered to show statistical significant differences between the two active dose groups (Exelon Patch 15cm^2 N = 237, Exelon Patch 10cm^2 N = 249). This analysis showed similar results to the main study. The subgroup

analysis of those patients with an MMSE ≥ 3 and ≤ 12 was likewise similar.

Severe Alzheimer's Dementia

Study US44 - 24 week controlled study

The efficacy of Exelon Patch in patients with severe dementia of the Alzheimer's type has been demonstrated in a 24-week double-blind study (8 weeks titration, 16 weeks maintenance on 15cm^2 patch) and its 24-week open-label extension phase (20 weeks of 15cm^2 treatment). Patients involved in the controlled study had at baseline an MMSE score of 3-12((~50% of patients had MMSE scores of < 10).
The mean age of patients was 77.0 years (range 51-96 years). Approximately 64.4% of patients were women and 35.6% of patients were men. The racial composition of the population was 87.3% Caucasian, and approximately 1.3% Oriental and 4.2% other. The study was designed to compare the efficacy of Exelon Patch 15 versus Exelon Patch 5 during a 24-week double-blind phase in severe Alzheimer's disease.

Table 4 Summary of Patient Demographics

Study #	Trial design	Dosage†, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
US44	Multicenter, randomized, double-blind, active (Exelon Patch 5)-controlled, parallel-group study.	Exelon Patch 5 (transdermal)	n=360	77.0 (51-96 years)	Male: 35.6% Female: 64.4%
		Exelon Patch 15 (trandermal) 24-week study	n=356		

Efficacy Measures

Efficacy was established by the use of independent, domain-specific assessment tools. These include the Severe Impairment Battery (SIB), the Alzheimer's Disease Cooperative Study Activity of Daily Living-Severe Impairment Version (ADCS-ADL-SIV) and the ADCS-CGIC. The SIB is a 40 item scale with a range of possible scores from 0 to 100, with higher scores reflecting higher levels of cognitive function. The ADCS-ADL-SIV is a caregiver-based scale consisting of 19 items designed to assess the patient's performance of both basic and instrumental activities of daily living, which had been used in several studies in moderate to severe Alzheimer's dementia. The total score ranges from 0 – 54, with higher scores indicating better function. The ADCS-CGIC is a comprehensive global assessment of the patient by the physician incorporating caregiver input.

Study Results

The Week 24 results for the two primary assessment tools are summarized in Table 5.

Table 5 Efficacy Results of the Week 24 Double-Blind Core Study (US44)

MFAS-LOCF population	**Exelon Patch 15** N = 338	**Exelon Patch 5** N = 335
SIB		
	(n=336)	(n=334)
Mean baseline ± SD	69.3 ± 21.54	68.3 ± 22.79
	(n=313)	(n=316)
Mean change at week 24 ± SD	-1.6 ± 13.54	-6.4 ± 14.01
LS Mean difference (95% CI)[1]	4.9 (2.80, 6.95)	
p-value[1]	<0.0001†	
ADCS-ADL-SIV		
	(n=333)	(n=319)
Mean baseline ± SD	29.7 ± 11.29	29.1 ± 11.94
	(n=310)	(n=303)
Mean change at week 24 ± SD	-2.6 ± 6.82	-3.6 ± 7.68
LS Mean difference (95% CI)[1]	1.2 (0.16, 2.32)	
p-value[1]	0.0247†	

† $p \leq 0.05$
MFAS: Modified Full Analysis Set.
LOCF: Last Observation Carried Forward.
LS: Least Squares.
[1] Obtained from an ANCOVA model with treatment and pooled center as factors, and baseline score (SIB or ADCS-ADL-SIV, respectively) as a covariate.

Figure 6 Change from Baseline in SIB Total Score (Study DUS44-MFAS–LOCF)

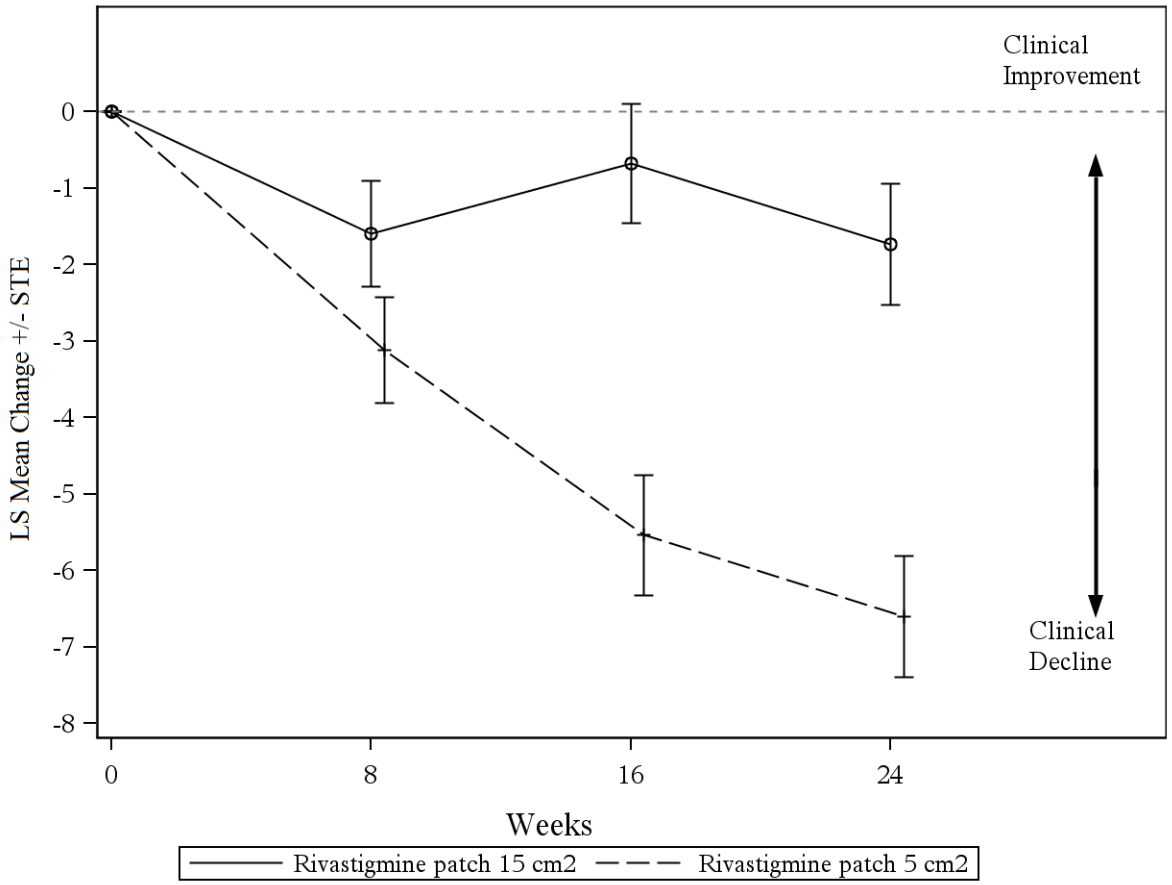
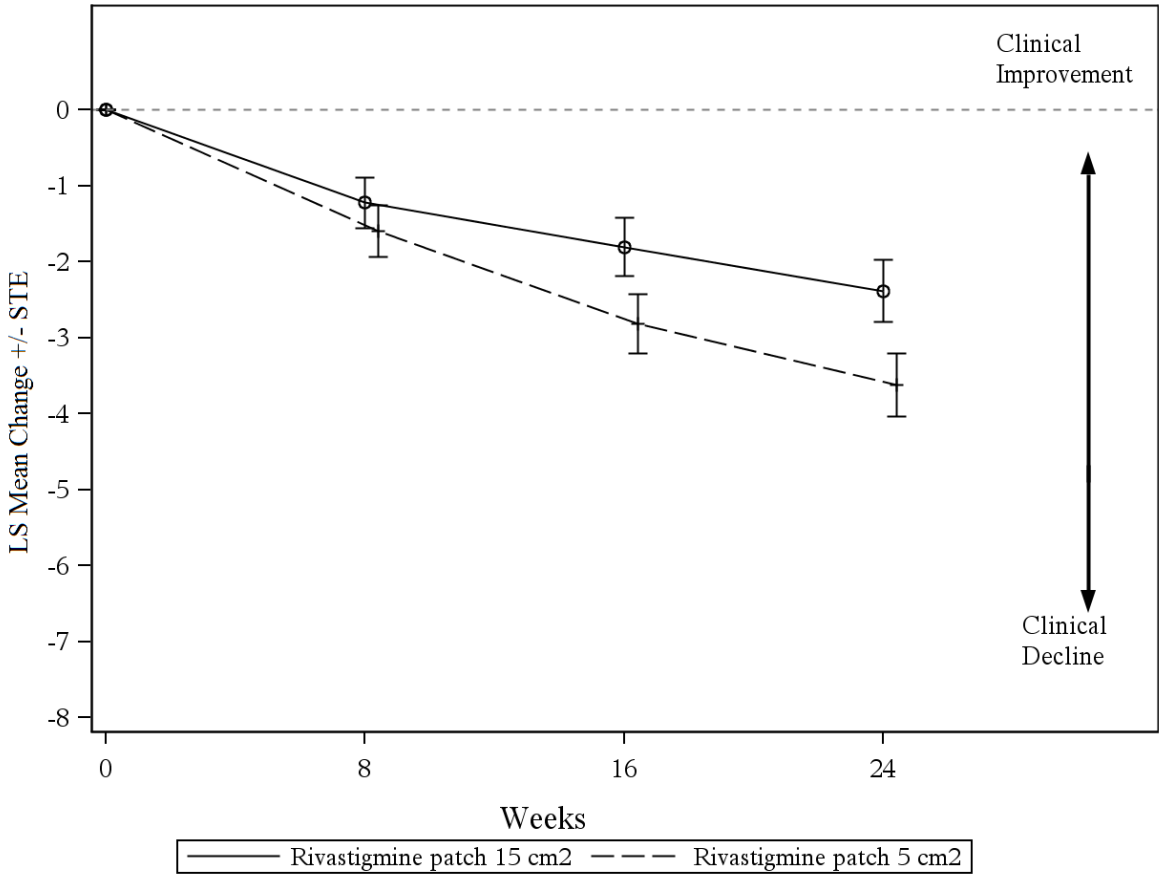


Figure 7 Change from Baseline in ADCS-ADL-SIV total score (Study DUS44-MFAS–LOCF)



Secondary Efficacy Measures

Results from the MFAS-LOCF analysis of the ADCS-CGIC showed significant benefit with regards to global functioning (mental/cognitive state, behavior, and functioning) at all time-points for patients treated with Exelon Patch 15 compared to patients who received Exelon Patch 5.

The NPI-12 scores are used to distinguish frequency and severity of psychiatric behavioural changes. Changes in NPI-12 scores from baseline and the between-group difference in these changes at all time-points were not statistically significant

INDICATIONS

Exelon is indicated for the treatment of patients with mild, moderate and severe dementia of the Alzheimer's type.

CONTRAINDICATIONS

The use of Exelon is contraindicated in patients with:

- known hypersensitivity to rivastigmine, to the excipients of the formulation, or to other carbamate derivatives.

- previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine transdermal patch (see “PRECAUTIONS – Application site and skin reactions”).
- severe liver impairment since it has not been studied in this population.

PRECAUTIONS

The incidence and severity of adverse reactions generally increase with increasing doses, particularly when the dose is increased. If treatment is interrupted for more than three days, it should be re-initiated with Exelon Patch 5 (see "DOSAGE and ADMINISTRATION").

Medication misuse and dosing errors resulting in an overdose

The previous day’s patch must be removed before applying a new one.

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 “OVERDOSAGE”). The majority of medication misuse and dosing errors have involved not removing the old patch when putting on a new one and the use of multiple patches at one time. Patients and their caregivers must be instructed on important administration instructions for Exelon patch (see “DOSAGE AND ADMINISTRATION”).

Gastrointestinal disorders:

The incidence and severity of adverse reactions generally increase with increasing doses, particularly at dose changes. 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, 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”).

In the controlled clinical trial [Study 2320], 7% of patients treated with the Exelon Patch 9.5 mg/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 9.5 mg/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 9.5 mg/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 9.5 mg/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 in patients with mild to moderate Alzheimer's dementia [Study 2320], 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.

Diarrhoea:

In the controlled clinical trial in patients with mild to moderate Alzheimer's dementia [Study 2320], 6% of the patients treated with the Exelon Patch 9.5 mg/24 hours developed diarrhoea, 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:

Patients with Alzheimer's disease may lose weight whilst taking rivastigmine. The patient's weight should be monitored during therapy with Exelon patches.

Patients with body weight below 50kg may experience more adverse events and may be more likely to discontinue due to adverse reactions. Carefully titrate and monitor these patients for adverse reactions (e.g. excessive nausea or vomiting) and consider reducing the dose if such adverse reactions develop (see DOSAGE AND ADMINISTRATION).

In the controlled clinical trial in patients with mild to moderate Alzheimer's dementia [Study 2320], 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 diarrhoea associated with the drug.

Anaesthesia:

Rivastigmine, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type relaxation during anaesthesia.

Application site and skin reactions:

Skin application site reactions may occur with Exelon Patch and are usually mild or moderate in intensity (see ADVERSE EFFECTS). 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 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 "CONTRAINDICATIONS"). Patients and caregivers should be instructed accordingly.

Extrapyramidal symptoms:

Like other cholinomemetics, rivastigmine may induce or exacerbate extrapyramidal symptoms. In patients with Parkinson's disease who were treated with rivastigmine capsules,

worsening of parkinsonian symptoms, especially tremor has been observed. Such adverse events may also occur with Exelon patches.

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 EFFECTS"). 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.

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 with active gastric or duodenal ulcers or predisposed to these conditions should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing gastric or duodenal 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 induce or 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 induce or 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.

Patients with body weight below 50 kg:
Caution should be exercised in titrating patients with body weight below 50 kg as these patients may experience more adverse reactions. Carefully titrate and monitor these patients for adverse reactions (e.g. excessive nausea and vomiting) and consider reducing the dose if such adverse reactions develop. See DOSAGE AND ADMINISTRATION.

Paediatric use

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. Patients with clinically significant hepatic impairment might experience more adverse reactions (see PHARMACOLOGY - Pharmacokinetics in hepatic impairment). Dosing recommendations to titrate according to individual tolerability should be closely followed. Particular caution should be exercised in titrating these patients above Exelon Patch 10. Exelon Patches are contraindicated in patients with severe liver impairment since they have not been studied in this population (see "CONTRAINDICATIONS").

Effects on ability to drive or operate machinery

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, 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 mammalians 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.

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.

Medicines 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

A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

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

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

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

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, CYP2C19 or CYP2B6.

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

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), 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 rivastigmine and these agents.

ADVERSE EFFECTS

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 6 lists treatment emergent signs and symptoms that were reported in at least 2% of patients with mild to moderate Alzheimer's dementia 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 6 Adverse drug reactions ≥ 2 % from the 24-week double-blind controlled clinical trial conducted with Exelon patch and capsules in patients with mild to moderate Alzheimer's dementia

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

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 6 may occur with Patch 5.

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

The following adverse drug reactions (From Sponsor's Review) were reported in patients with severe Alzheimer's dementia treated with Exelon patch 15.

Table 7 Adverse drug reactions (From Sponsor's Review ≥5% in either Exelon Patch groups) from the 24 week (16 weeks of 15cm^2 patch treatment) double-blind randomized controlled clinical trial conducted with Exelon patch 15 in patients with severe Alzheimer's dementia

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

Table 8 details adverse events which were thought to be related to Exelon Patch by the reporting investigator for DUS44 using the cut off of 2 %.

Table 8 Summary of adverse events suspected by the investigator to be related to Exelon Patch (at least 2% in any treatment group) (Study DUS44-Safety set)

Preferred term	Exelon Patch 15 N=355 n (%)	Exelon Patch 5 N=359 n (%)
Total number of patients with AE(s)	146 (41.1)	132 (36.8)
Application site erythema	45 (12.7)	39 (10.9)
Application site dermatitis	27 (7.6)	31 (8.6)
Nausea	16 (4.5)	9 (2.5)
Vomiting	15 (4.2)	6 (1.7)
Weight decreased	15 (4.2)	9 (2.5)

Application site pruritus	13 (3.7)	8 (2.2)
Application site irritation	11 (3.1)	9 (2.5)
Decreased appetite	10 (2.8)	3 (0.8)
Agitation	10 (2.8)	6 (1.7)
Diarrhea	9 (2.5)	12 (3.3)
Somnolence	9 (2.5)	4 (1.1)
Application site oedema	6 (1.7)	4 (1.1)

Source: Study DUS44-PT Table 14.3.1-1.4

Table 9 shows the adverse events (≥2% in Exelon Patch groups) from the 48-week double-blind clinical trial observed in subpopulation of patients with moderate to severe Alzheimer's dementia treated with Exelon Patch 15.

Table 9 Adverse Events (≥2% in either Exelon Patch Group) from the 48-Week Double-Blind Randomized Controlled Clinical Trial Conducted with Exelon Patch 15 in Subpopulation of Patients with Moderate to Severe Alzheimer's Disease

	Cummulative (Week 0-48)		**Week 0 to 24**		**Week > 24 to 48**	
	Exelon Patch 15 N = 252	**Exelon Patch 10 N = 260**	**Exelon Patch 15 N = 252**	**Exelon Patch 10 N = 260**	**Exelon Patch 15 N = 215**	**Exelon Patch 10 N = 226**
Total percentage of patients with AE(s)	74	67	64	54	43	39
Gastrointestinal Disorders						
Nausea	12	4	10	3	4	2
Vomiting	11	5	10	3	2	3
Diarrhea	6	5	4	4	0	0
Abdominal pain upper	3	1	2	1	0	0
Constipation	3	2	1	2	2	0
General Disorders and Administration Site Conditions						
Application site erythema	7	5	6	4	0	0
Fall	7	7	4	4	3	3
Application site pruritus	4	4	3	3	0	0
Edema peripheral	3	3	2	2	2	1
Infections and infestations						
Urinary tract infection	6	4	3	2	4	2
Nasopharyngitis	3	2	2	1	0	0
Investigations						
Weight decreased	7	3	3	2	6	2
Metabolism and Nutritional Disorders						
Decreased appetite	6	3	6	2	0	0
Dehydration	3	2	2	1	0	0
Nervous System Disorders						
Headache	4	4	4	3	0	0
Dizziness	4	0	3	0	0	0
Syncope	3	2	1	1	2	1

Psychomotor hyperactivity	3	4	2	3	0	0
Psychiatric Disorders						
Agitation	6	6	4	4	1	3
Depression	5	5	2	3	3	2
Anxiety	4	3	2	2	0	0
Insomnia	4	3	1	1	3	2
Renal and Urinary Disorders						
Urinary incontinence	4	2	2	1	0	0
Vascular Disorders						
Hypertension	3	3	2	2	0	0
Hypotension	3	1	2	1	1	0

Application site reactions (skin irritation):

In the 24-week double-blind study [Study 2320], 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. In clinical trials in a Chinese population and a Japanese population discontinuations for skin reactions in the groups receiving Exelon patch were 4.9% and 8.4% respectively.

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.

In the 48-week active controlled clinical trial [Study 2340], cases of skin irritation were captured as patient or caregiver reported adverse events. The most commonly reported skin irritation events during the first 24 weeks of the double-blind period for Exelon Patch 15 group and Exelon Patch 10 group, respectively were application site erythema (5.7% vs. 4.6%) and application site pruritus (3.6% vs. 2.8%). The percentages decreased in both Exelon Patch 15 and Exelon Patch 10 treatment groups over time (>24 weeks): application site erythema (0.8% vs. 1.6%) and application site pruritus (0.4% vs. 1.2%), respectively. Application site pruritus led to discontinuation in 1.1% of the patients from each of the treatment groups during the total 48 week double-blind treatment phase. Application site reactions were mostly mild or moderate in severity and were rated as severe in less than 2% of patients.

In the 24-week double-blind, double-dummy, controlled clinical trial in patients with severe Alzheimer's disease [Study US44], cases of skin irritation were captured as adverse events. The most commonly reported skin irritation events for Exelon Patch 15 and Exelon Patch 5, respectively were application site erythema (13.2% vs. 11.7%), application site dermatitis (7.6% vs 9.2%) and application site pruritus (3.7% vs. 2.2%). Application site erythema led to discontinuation in only 0.8% of the patients in 15 cm^2 group and in 0.6% of patients in 5 cm^2 group. Application site erythema in both groups was mostly mild or moderate in severity.

See 'PRECAUTIONS - Application site and skin reactions.

A direct comparison of the rate of skin irritation events reported in each of these studies cannot be made due to the difference in data collection methods employed.

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).

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

Table 10 Adverse drug reactions reported in 2687 patients with Alzheimer's dementia treated for 24 weeks to 48 weeks in randomized controlled clinical studies with Exelon Patch 5, Exelon Patch 10, Exelon patch 15 and Exelon Patch 20[1].

Metabolism and nutrition disorders	
Common	Anorexia, decreased appetite
Uncommon	Dehydration
Psychiatric disorders	
Common	Anxiety, depression, delirium, insomnia
Uncommon:	Agitation, hallucinations, aggression
Nervous system disorders	
Common:	Dizziness, headache, syncope
Uncommon:	Cerebrovascular accident, somnolence*, psychomotor hyperactivity
	Extrapyramidal symptoms
Very rare	
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. hemorrhagic duodenitis)
Renal and urinary disorders	
Common	Urinary incontinence
Skin and subcutaneous tissue disorders	
Common:	Rash
Uncommon:	Hyperhidrosis
General disorders and administration site conditions	
Common:	Application site reactions, application site erythema**, application site pruritus**, application site oedema**, application site dermatitis, application site irritation, fatigue, asthenia, pyrexia
Uncommon:	Contact dermatitis**, malaise
Rare	Fall

Investigations	
Common:	Weight decrease
Infections and infestations	
Common	Urinary tract infection

[1]Exelon Patch 20 is not registered in Australia

*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”.

Additional Adverse Drug Reactions from Post-marketing spontaneous reports

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

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

Very rarely reported: tachycardia, atrioventricular block, atrial fibrillation, pancreatitis, seizure

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

Additional Adverse Drug Reactions which have been reported with rivastigmine capsules or oral solution

Very rare: severe vomiting associated with oesophageal rupture.

Rare: angina pectoris, myocardial infarction, duodenal ulcers.

Common: confusion.

DOSAGE AND ADMINISTRATION

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 be replaced by a new one after 24 hours.

The patch should not be used with any other acetylcholinesterase inhibitors (see “INTERACTIONS WITH OTHER MEDICINES”).

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 “PRECAUTIONS” and “OVERDOSAGE”).
- 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 general 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 to the same site for the rest of the 24hours, then it should be replaced at the same time as usual the next day.
- The patch can be used in everyday situations, including bathing and during hot weather.
- The patch should not be exposed to any external heat sources (e.g. excessive sunlight, saunas, solarium) for long periods of time.
- The patch should not be cut into pieces.
- Wash your hands with soap and water after removing the patch. In case of contact with eyes or if the eyes become red after handling the patch, rinse immediately with plenty of water and seek medical advice if symptoms do not resolve.

Dosage

Initial dose and dose titration to the effective dose

Treatment is started with Exelon Patch 5 once a day.

Increase the dose only after a minimum of 4 weeks at the previous dose, and only if the previous dose has been well tolerated. For mild and moderate Alzheimer's disease patients continue the recommended effective dose of Exelon Patch 10 for as long as therapeutic benefit persists. Moderate patients can then be increased to the maximum recommended dose of Exelon Patch 15. For patients with severe Alzheimer's disease, after titration up Exelon Patch 15 may be used. Doses higher than Exelon Patch 15 confer no appreciable additional benefit, and are associated with an increase in the incidence of adverse events.

Maintenance dose

Mild Alzheimer's Disease
The effective dosage is Exelon Patch 10 administered once per day; replace with a new patch every 24 hours.

Moderate Alzheimer's Disease

After 4 weeks on Patch 5, if tolerated increase to Patch 10. The effective dosage is Exelon Patch 10 for as long as therapeutic benefit persists but (after a minimum of 4 weeks) this may be increased to Exelon Patch 15 administered once per day; replace with a new patch every 24 hours.

Severe Alzheimer's Disease

After a minimum 4 weeks on Patch 5 if tolerated increase to Patch 10. If this is tolerated for a further 4 weeks then Exelon Patch 15 administered once per day; replace with a new patch every 24 hours.

Interruption of treatment:

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 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 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 9 mg 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 please see instructions for dose titration to the effective dose in DOSAGE AND ADMINISTRATION section.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. Patients with clinically significant hepatic impairment may experience more dose dependent adverse reactions. (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”). Exercise caution when up-titrating patients below 50 kg body weight as these patients may experience more adverse reactions. Carefully titrate and monitor these patients for adverse reactions (e.g. excessive nausea or vomiting) and consider reducing the dose if such adverse reactions develop.

OVERDOSAGE

Symptoms

Most cases of accidental overdosage 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, 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, 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.

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. 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 1 hour and 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.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Three strengths of Exelon patches are available, providing the following in vivo release rates.

Patches	Surface area cm^2	Rivastigmine base dose load	Rivastigmine base *in vivo* release rates per 24 h
Exelon Patch 5	5	9 mg	4.6 mg
Exelon Patch 10	10	18 mg	9.5 mg
Exelon Patch 15	15	27 mg	13.3 mg

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 7 or 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.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (Schedule 4).

DATE OF FIRST INCLUSION IN AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

12 March 2008

DATE OF MOST RECENT AMENDMENT

8 June 2016

Internal Document Code

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