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EMA/81748/2014
Committee for Medicinal Products for Human Use (CHMP)

Exelon/Prometax

(Rivastigmine)

Procedure No. EMEA/H/C/xxxx/WS/0355

Marketing authorisation holder: Novartis Europharm Ltd

Withdrawal Assessment report for an extension of indication

This withdrawal Assessment Report is based on the latest assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.
This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still on-going at the time of the withdrawal of the application.

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LIST OF ABBREVIATIONS

AChE	Acetylcholinesterase
AD	Alzheimer's disease / Alzheimer's dementia
ADL	Activity of Daily Living
ADAS-cog	Alzheimer's disease Assessment Scale – cognitive subscale
ADCS-ADL	Alzheimer's disease Cooperative Study – Activities of Daily Living scale
ADCS-Instrumental ADL	Alzheimer's disease Cooperative Study – Instrumental Activities of Daily Living subscale
ADCS-CGIC	Alzheimer's Disease Cooperative Study- Clinical Global Impression of Change
AE	adverse event
ANCOVA	analysis of covariance
BuChE	Butyrylcholinesterase
CI	confidence interval
DB	double-blind
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECG	electrocardiogram
EMA/EMEA	European Medicines Agency
ENA713	Exelon® (rivastigmine)
FDA	Food and Drug administration
ITT	intent to treat population
ITT-DB	intent to treat double-blind phase population
LOCF	last observation carried forward
MAR	missing at random
MFAS	Modified full analysis set
MMRM	mixed-effects repeated measures model
MMSE	Mini-Mental State Examination Scores
NDA	new drug application
NMDA	N-methyl-D-aspartate
NPI-12	Neuropsychiatric inventory (12 items)
SAE	serious adverse event
SCE	Summary of Clinical Efficacy
SE	Standard Error
SIB	Severe Impairment Battery
SPA	Special Protocol Assessment
US	United States

1. EXECUTIVE SUMMARY

1.1. Problem statement

Alzheimer's disease is a progressive disease. The currently available treatment options are authorised for the symptomatic treatment of dementia and are not believed to impart any disease modifying effect on the progressive neurodegenerative nature of the disease.

The once-daily rivastigmine transdermal patches 4.6 mg/24h (5 cm2) and 9.5 mg/24h (10 cm2) were approved in the EU for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer's type on 17-Sep-2007. CHMP granted a positive opinion for the rivastigmine patch 13.3 mg/24 h for the treatment of mild to moderately severe Alzheimer disease (AD) on 15-Nov-2012, given that the recommended maintenance dose 9.5 mg/24 h is well tolerated and given that the patient have demonstrated a meaningful cognitive aggravation (e.g. decrease in the MMSE) and/or functional decline (based on physician judgement) while on the recommended daily maintenance dose of 9.5mg/24h.

The present type II variation proposed to extend the indication for the Exelon patch to include the *"Symptomatic treatment of severe Alzheimer's dementia"*.

To support the current application and in order to determine if patients with severe dementia of the Alzheimer's type would benefit from rivastigmine patch, study ENA713DUS44 and ENA713DUS44E1 were designed to investigate the efficacy and safety of rivastigmine transdermal patches 13.3 mg/24 h (15 cm2) patch compared to rivastigmine transdermal patches 4.6 mg/24h (5 cm2) in patients with severe AD.

1.2. About the product

Exelon/Prometax (rivastigmine) is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease and Parkinson's disease.

Rivastigmine interacts with its target enzymes by forming a covalently bound complex that temporarily inactivates the enzymes.

A smooth fall in plasma BuChE activity was seen after the administration of all four patch sizes. Plasma BuChE activity decreased slowly with maximum inhibition after approximately 16, 12, 8, and 8 hours after application of the 5, 10, 15, and 20 cm2 patches, respectively. BuChE activity was then sustained over the remainder of the 24-h patch application period. Within 16 hours of removal of the last patch (i.e.; 40 hours after the last application) BuChE activity returned to the base levels seen with the lowest patch dose.

1.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

No Scientific advice has been given in relation to the development of the new indication. Overall, CHMP guideline for AD has been followed.

1.4. General comments on compliance with GCP

The studies ENA713DUS44 and ENA713DUS44E1 were conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents, according to the applicant.

1.5. Type of application and other comments on the submitted dossier

This is a central application, made pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novartis submitted to the European Medicines Agency an application for a variation including an extension of indication.

An updated version of the Risk Management Plan for this line extension has been submitted.

The proposed PIL is similar in its content to the currently approved patches. The Applicant did not submit a new user testing, which is considered as acceptable.

Concerning paediatric studies, a class waiver has been granted for Alzheimer's disease (EMA/PDCO/806338/2010).

2. SCIENTIFIC OVERVIEW AND DISCUSSION

2.1. Quality aspects

Drug substance – Drug Product

No data on the drug substance or drug product is included in the dossier. It is acceptable for extension of indication application.

2.2. Non clinical aspects

No new preclinical data has been included for this extension of indication, which was considered acceptable.

2.3. Clinical aspects

Pharmacokinetics

No PK studies specific to the current variation application have been submitted and the applicant refers to previous studies conducted with Exelon transdermal patch.
The population with severe AD may be older, more fragile and probably of lower weight than the presently approved population with mild to moderate AD. However, based on previous information, age had no impact on the exposure to rivastigmine in Alzheimer's disease patients treated with Exelon transdermal patches. For the oral formulations it was concluded that even if bioavailability of rivastigmine is greater in elderly than in young healthy volunteers, studies in Alzheimer patients aged between 50 and 92 years showed no change in bioavailability with age.

Pharmacodynamics

No new pharmacology study has been submitted in this application.

Exelon/Prometax (rivastigmine) is a slowly reversible (pseudo-irreversible), dual inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) of the carbamate type. Exelon exerts its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible cholinesterase inhibition.

There is evidence that severe AD may be correlated to the presence of more profound cholinergic deficit over time (Hanyu et al, AJNR Am J Neuroradiol 23:27–32, January 2002). Additionally, acetylcholinesterase (AChE) activity is known to decrease by as much as 85% during the course of the disease while butyrylcholinesterase (BuChE) activity remains unaltered or may even increase (Naik et al, J Pharm Pharmaceut Sci 12 (1): 79 - 85, 2009).

The relationship between plasma concentration and effect for rivastigmine in severe AD has not been discussed. There is a claimed higher cholinergic deficit in patients with severe AD dementia compared to patients with mild to moderate AD. The PK/PD relationship may be different in this patient group, however, due to lack of data no conclusions may be drawn.

- **Tabular overview of clinical studies**

Overview of trials or sources of data

Source of data	Details
Dose-selection trials	Dose selection was based on data previously submitted in **Study CENA713 D2320**
Controlled trials	**Study CENA713 DUS44:** double-blind, randomized, active-controlled trial with Exelon 15 and 5 cm_2 patches (24-week efficacy data)
Uncontrolled trails	**Study CENA713 DUS44E1:** open-label extension (24-week)
Other sources of efficacy data	**Study CENA713 D2320:** post-hoc analysis of the subset of severe AD patients from the double-blind phase.
Trials used for combined efficacy analysis	Not applicable

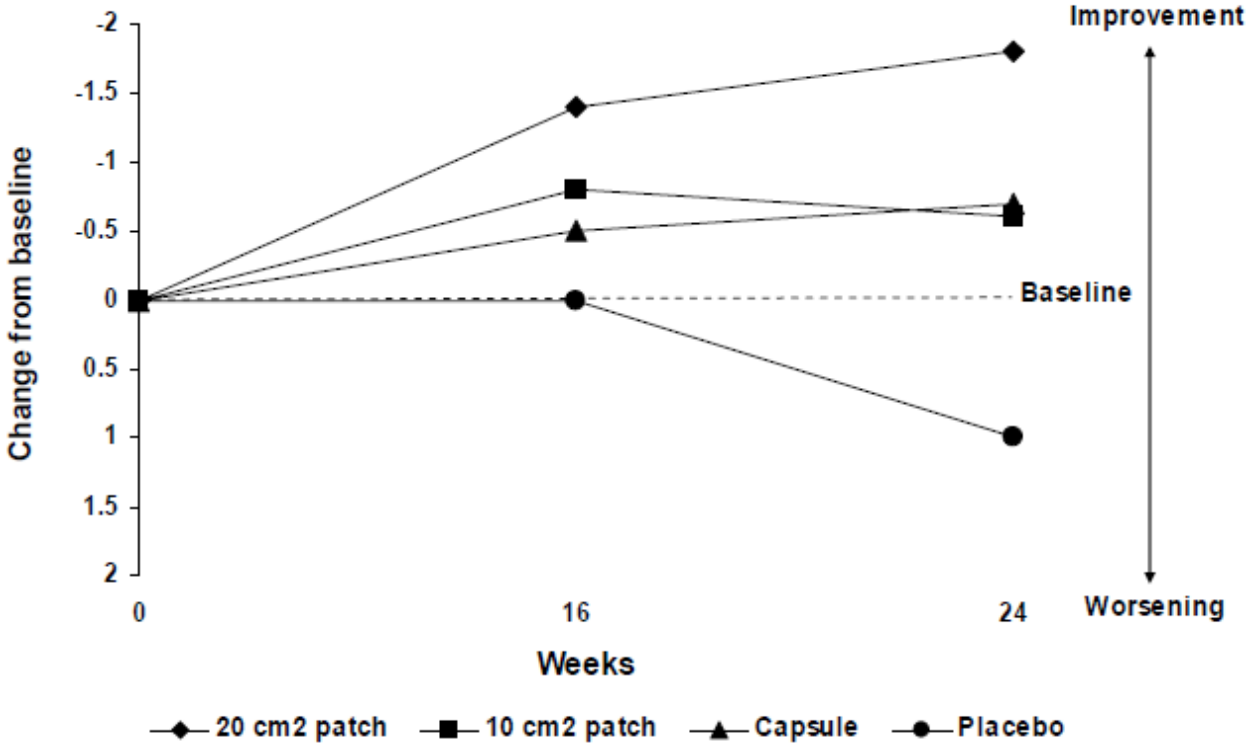
Clinical efficacy

Dose-response study

The selection of the rivastigmine 15 cm2 patch for severe AD patients was based on the results from study D2320 previously submitted in EMEA/H/C/0169/X/38 and EMEA/H/C/0255/X/39, showing the evidence for a dose response (Figure 3-1) and a potentially better safety GI profile of higher dosage strengths of the rivastigmine patch in the more severe patients, compared to patients with mild to moderate AD (Table 3-4).

Study D2320 was a 24-week, multicenter, randomized, double-blind, placebo- and active controlled, parallel-group study. Four treatment arms (placebo, 10 cm2 patch, 20 cm2 patch and 6 mg/bid capsules) were included. Patients were to be titrated to their target (or maximum tolerated) dose of rivastigmine patch or capsule in four consecutive ascending dose levels with step titrations occurring every 4 weeks until the targeted or highest tolerated dose was achieved. The change from baseline in ADAS-cog total score for the 20 cm2 group compared to placebo was statistically significant at Week 24 and numerically favored the 20 cm2 group over the 10 cm2 patch group by 1.0 point (p=0.073) showing a probable dose response for cognition (Figure 3-1).

Figure 3-1 Change from baseline at 24 weeks on the ADAS-cog – (ITT-OC)



However, at that time the CHMP concluded that the benefit-risk of the 20 cm2 patch was unfavourable. This conclusion was based on a dose response relationship of the incidence of AEs in patients in the higher and lower patch size groups, for gastrointestinal AEs (nausea, vomiting, diarrhoea, decreased weight, decreased appetite, anorexia), for asthenia, and for nervous system AEs (dizziness, insomnia, agitation) and more cardiac disorders and higher incidence of serious adverse events when treated with the 20 cm2 patch compared to other treatment groups (EMEA/H/C/000169/X/0038 and EMEA/H/C/00255/X/0039).

Retrospective safety analysis by the Applicant of GI AEs in the subgroups of more severe and less severe patients in study D2320, indicate that more severe patients might experience fewer GI side effects, which potentially could be explained by a greater cholinergic deficit (Table 3-4).

Table 3-4 Adverse events of interest (nausea, vomiting) regardless of study drug relationship by preferred term, treatment and MMSE severity (<15 and >=15) (Study D2320) - Safety population

	MMSE < 15				MMSE ≥ 15			
	Rivastigmine				Rivastigmine			
Preferred term	Patch 20 cm^2 N= 75 %	Patch 10 cm^2 N= 68 %	Capsule N= 89 %	Placebo N= 88 %	Patch 20 cm^2 N= 228 %	Patch 10 cm^2 N= 222 %	Capsule N= 205 %	Placebo N= 213 %
Vomiting	16.0	5.9	14.6	5.7	19.7	6.3	18.0	2.3
Nausea	17.3	5.9	20.2	4.5	22.4	7.7	24.4	5.2

In addition to the effect on efficacy and safety described above, the Applicant has chosen to test the 13.3 mg/24 h dosage strength in patients with severe AD also taking into account the claimed higher cholinergic deficit in patients with severe AD dementia, compared to mild to moderate dementia of AD.

Main clinical studies

Study ENA713DUS44 was a 24-week prospective, randomized, parallel-group, double-blind, multicenter study comparing the effects of rivastigmine patch 15 cm2 *versus* rivastigmine patch 5 cm2 on ACTivities of daily living and cogniTION in patients with severe dementia of Alzheimer's type (ACTION).

Unlike other trials in severe dementia of the Alzheimer's type, study DUS44 used as a comparator the rivastigmine 5 cm2 patch instead of placebo. The primary reason for using a low dosage strength arm was to ensure greater feasibility, based on previous experience with the use of a placebo which resulted in a low completion rate.

The study consisted of 3 periods (pre-randomization, randomization, double-blind treatment) with a total of 8 visits. Eligible patients were randomized in a 1:1 ratio to rivastigmine 13.3 mg/24 h (15 cm2) patch or rivastigmine 4.6 mg/24 h (5 cm2) patch.

All patients received a daily dose of rivastigmine 4.6 mg/24 h applied in a 5 cm2 patch for a 4-week period. After 4 weeks on this dose, patients assigned to the 15 cm2 patch group were up-titrated from the 4.6 mg/24 h (5 cm2) patch to the 9.5 mg/24 h (10 cm2) patch, and patients randomized to the 4.6 mg/24 h (5 cm2) patch group remained at that dose.
To maintain blinding, patients in each group were also given placebo patches corresponding to the sizes of the active doses of the other treatment group (5 cm2 and 10 cm2, respectively).

Patients remained on these doses for another 4-week period.

At the second titration visit (Week 8), the dose of study drug was increased again to the target dose of 13.3 mg/24 h (15 cm2) for patients randomized to the 15 cm2 patch group and continued at 4.6 mg/24 h (5 cm2) for patients randomized to the 5 cm2 patch group. Placebo patches corresponding to the sizes of the active doses in the other treatment group were also given (5 m2 and 15 cm2, respectively). All patients were maintained at the target doses for the 16-week maintenance period of the study.

Period	Pre-randomization		Double-blind Treatment						
	Screening	Baseline	First Dose	Titration		Maintenance			
Week	-4 to -1	Day 0	Day 1	4	8	12	16	20	24
Visit	1	2		3	4	5	6	7	8
		⇧ Randomization							
TX Arm 1: rivastigmine + placebo			5 cm^2	10 cm^2 + 5 cm^2		15 cm^2 + 5 cm^2			
TX Arm 1: rivastigmine + placebo			5 cm^2	5 cm^2 + 10 cm^2		5 cm^2 + 15 cm			
Efficacy Assessments performed		↑			↑		↑		↑

TX=treatment; 5 cm^2 patch=4.6 mg/24 hours; 10 cm^2=9.5 mg/24 hours;15 cm^2=13.3 mg/24 hours

The primary objectives were:

- To compare the effect of rivastigmine patch 13.3 mg/24 hours (h) (15 cm2) vs. rivastigmine patch 4.6 mg/24 h (5 cm2) on activities of daily living assessed using the Alzheimer's Disease Cooperative Study-Activities of Daily Living-Severe Impairment Version (ADCS-ADL-SIV).
- To compare the effect of rivastigmine patch 13.3 mg/24 h (15 cm2) vs. rivastigmine patch 4.6 mg/24 h (5 cm2) on cognition assessed using the Severe Impairment Battery (SIB) at 24 weeks**.**

The secondary objectives were:

• To compare the effect of rivastigmine patch 13.3 mg/24 h (15 cm2) vs. rivastigmine patch 4.6 mg/24 h (5 cm2) on behavior assessed using the Neuropsychiatric Inventory-12 (NPI-12).

• To compare the effect of rivastigmine patch 13.3 mg/24 h (15 cm2) vs. rivastigmine patch 4.6 mg/24 h (5 cm2) on global functioning assessed using the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC).
• To assess the safety and tolerability of the 13.3 mg/24 h (15 cm2) rivastigmine patch formulation.

The exploratory objective of this study was:
• To compare response rates defined by change from baseline in ADCS-ADL-SIV, SIB, NPI-12 and ADCS-CGIC.

The study population consisted of male and female outpatients 50 years or older with a clinical diagnosis of probable severe dementia of the Alzheimer's type based on National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) and an MMSE score of > 3 and < 12, inclusive.

Patients were excluded if they have a current diagnosis of probable vascular dementia, according to National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria, if they were diagnosed with an advanced, severe, progressive, or unstable disease of any type that may have interfered with efficacy and safety assessments or put the patient at special risk, any current medical or neurological condition other than AD that could explain the patient's dementia (e.g., abnormal thyroid function tests, Vitamin B12 or folate deficiency, post-traumatic conditions, Huntington's disease, Parkinson's disease, syphilis) or any other DSM-IV Axis 1 diagnosis that could have interfered with the evaluation of the patient's response to study medication, including other primary neurodegenerative dementia, schizophrenia, or bipolar disorder.

The co-primary efficacy variables were:
The changes from baseline in the Alzheimer's Disease Cooperative Study-Activities of Daily Living – Severe Impairment Version (ADCS-ADL-SIV) total score, which is the sum of 19 items with higher scores representing higher functioning of the patient and,
Severity Impairment Battery (SIB) total score which is the sum of 40 items with higher scores reflecting higher levels of cognitive ability.

Secondary efficacy variables were: The Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) score and the change from baseline in the Neuropsychiatric Inventory (NPI-12) score were secondary efficacy variables.

A total of 716 patients were randomized at 82 centres in the United States.

A total of 463 (64.7%) of the 716 patients randomized completed the study: 229 (64.3%) in the rivastigmine 13.3 mg/24 h (15 cm2) patch group and 234 (65.0%) in the rivastigmine 4.6 mg/24 h (5 cm2) patch group. One death occurred in each group during the study.

Adverse events were the most common reason for discontinuation from the study in both groups, with more patients (20.5%) at the higher dose discontinuing for this reason than at the lower dose (14.2%). Withdrawal of consent was the second most common reason for discontinuation, accounting for more discontinuations at the lower dose (12.8%) than at the higher dose (7.6%). Unsatisfactory therapeutic effect accounted for <4% of discontinuations in each treatment group.

Table 10-1 Patient disposition (all patients)

	Rivastigmine patch		
	13.3 mg/24 h (15 cm^2) (N=356)	4.6 mg/24 h (5 cm^2) (N= 360)	Total (N= 716)
Disposition/Reason	**n (%)**	**n (%)**	**n (%)**
Total number of patients			
Screened			1014
Screened, not randomized			298
Randomized	356 (100.0)	360 (100.0)	716 (100.0)
Exposed to study medication	355 (99.7)	359 (99.7)	714 (99.7)
Completed	229 (64.3)	234 (65.0)	463 (64.7)
Discontinued from study	127 (35.7)	126 (35.0)	253 (35.3)
Primary reason for study discontinuation			
Adverse events	73 (20.5)	51 (14.2)	124 (17.3)
Abnormal laboratory values	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal test procedure results	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	13 (3.7)	14 (3.9)	27 (3.8)
Patient's condition no longer required study drug	0 (0.0)	0 (0.0)	0 (0.0)
Patient withdrew consent	27 (7.6)	46 (12.8)	73 (10.2)
Lost to follow-up	3 (0.8)	2 (0.6)	5 (0.7)
Administrative problems	2 (0.6)	2 (0.6)	4 (0.6)
Death	1 (0.3)	1 (0.3)	2 (0.3)
Protocol deviation	8 (2.2)	10 (2.8)	18 (2.5)

There were no statistically significant differences between treatment groups in any of the baseline or demographic characteristics. The majority of patients were female and Caucasian. Mean ages were comparable between groups, but slightly more patients were older than 75 years and slightly fewer patients younger than 65 years in the higher dose group.

Table 11-2 Baseline and demographic summary by treatment group (Randomized set)

	Rivastigmine patch			
	13.3 mg/24 h (15 cm^2)	4.6 mg/24 h (5 cm^2)	Total	
Demographic variable	**(N=356)**	**(N= 360)**	**(N= 716)**	**p-value**
Age (years)				0.1040[a]
N	356	360	716	
Mean (SD)	77.6 (8.69)	76.5 (9.35)	77.0 (9.04)	
Median	78.0	78.0	78.0	
(Min, Max)	(52, 96)	(51, 96)	(51, 96)	
Age group (years) – n (%)				0.2553[b]
<65 years	33 (9.3)	45 (12.5)	78 (10.9)	
65–75 years	93 (26.1)	101 (28.1)	194 (27.1)	
> 75	230 (64.6)	214 (59.4)	444 (62.0)	
Gender – n (%)				0.7299[b]
Male	129 (36.2)	126 (35.0)	255 (35.6)	
Female	227 (63.8)	234 (65.0)	461 (64.4)	

There were no statistically significant differences between treatment groups in any of the background variables. Approximately 90% of patients enrolled in the study were living at home; a

similar percentage had received prior treatment for AD. The mean period since diagnosis of AD was approximately 4 years and the mean period since diagnosis of severe dementia was approximately 1 year. The mean scores in Mini Mental State Examination were in both groups 8.8.

Table 11-3 Background information (Randomized set)

	Rivastigmine patch			
	13.3 mg/24 h (15 cm^2) (N=356)	4.6 mg/24 h (5 cm^2) (N= 360)	Total (N= 716)	p-value
Patient's living situation – n (%)				0.5793[a]
Home	322 (90.4)	317 (88.1)	639 (89.2)	
Assisted living facility	27 (7.6)	35 (9.7)	62 (8.7)	
Other	7 (2.0)	8 (2.2)	15 (2.1)	
Has patient been treated for AD – n (%)				1.0000[a]
Yes	325 (91.3)	328 (91.1)	653 (91.2)	
No	31 (8.7)	32 (8.9)	63 (8.8)	
Time since diagnosis of AD (years)				0.2714[b]
n	356	360	716	
Mean (SD)	4.25 (2.709)	4.03 (2.666)	4.14 (2.688)	
Median	3.94	3.73	3.85	
(Min, Max)	(0.0, 19.1)	(0.0, 18.3)	(0.0, 19.1)	
Time since diagnosis of severe dementia (years)				0.5959[b]
n	356	360	716	
Mean (SD)	1.22 (1.876)	1.15 (1.609)	1.18 (1.746)	
Median	0.54	0.46	0.50	
(Min, Max)	(0.0, 12.2)	(0.0, 9.8)	(0.0, 12.2)	
Mini Mental State Examination score				0.9861[b]
n	356	360	716	
Mean (SD)	8.84 (2.863)	8.84 (2.951)	8.84 (2.905)	
Median	10.00	9.00	10.00	
(Min, Max)	(3.0, 13.0)	(3.0, 19.0)	(3.0, 19.0)	

AD=Alzheimer's Disease; SD= standard deviation

[a]From a Fisher's exact test (excluding missing values), comparing the 2 treatment groups

[b]From a 2-sample t-test comparing the 2 treatment groups

The number of randomized patients in the Safety set and the MFAS were similar between treatment groups. One randomized patient in each group was excluded from the Safety set. A total of 18 randomized patients in the 13.3 mg/24 h (15 cm2) patch group and 25 in the 4.6 mg/h (5 cm2) patch group were excluded from the MFAS.

Table 11-1 Analysis sets (all randomized patients)

Analysis patient set	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=356) n (%)	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N= 360) n (%)	Total (N= 716) n (%)
Randomized set[a]	356 (100.0)	360 (100.0)	716 (100.0)
Safety set[b]	355 (99.7)	359 (99.7)	714 (99.7)
Modified Full Analysis set[c]	338 (94.9)	335 (93.1)	673 (94.0)

Note: The denominator for the percentages is the number of subjects randomized.

[a]All patients randomized were included in the Randomized set.

[b]The Safety set included all patients who received at least 1 dose of study medication and had at least 1 safety assessment after baseline. The statement that a patient had no adverse events constituted a safety assessment.

[c]Modified full analysis set comprised all randomized patients who received at least 1 dose of study medication and had at least 1 post-baseline measurement of the co-primary efficacy variables. Patients inappropriately randomized were excluded from this analysis set.

- **Outcomes**

Summary of main study

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial ENA713DUS44

Title: A 24 Week, Prospective, Randomized, Parallel-Group, Double-Blind, Multi-Center Study Comparing the Effects of Rivastigmine Patch 15 cm2 vs. Rivastigmine Patch 5 cm2 on ACTivities of Daily Living and CognitION in Patients with Severe Dementia of the Alzheimer's Type (ACTION)			
Study identifier	ENA713DUS44		
Design	Prospective, Randomized, Parallel-Group, Double-Blind		
	Duration of titration phase: Duration of double-blind phase: Duration of extension phase:		8 weeks 16 weeks 24 weeks
Hypothesis	Superiority		
Treatment groups	Rivastigmine 15 cm2		number randomised: 356
	Rivastigmine 5 cm2		number randomised: 360
Endpoints and definitions	Co- Primary endpoint	ADCS-ADL-SIV SIB	Changes from baseline
	Secondary endpoint	NPI-12 ADCS-CGIC	Changes from baseline
	other endpoint	Response rate	Defined by change from baseline in ADCS-ADL-SIV, SIB, NPI-12 and ADCS-CGIC

Database lock	10-01-2012			
Results and analysis				
Analysis description	**Primary analysis**			
Analysis population and time point description	Analyzed population was the Modified Full Set Analysis Set (MFAS). Primary and secondary endpoints were analyzed at baseline, Week 8, Week16 and Week 24			
Descriptive statistics and estimate variability	Treatment group	Rivastigmine 13.3 mg/24h (15 cm2)	Rivastigmine (4.6 mg/24h (5 cm2)	13.3 mg vs 4.6 mg
	Number of subjects	338	335	
	ADCS-ADL-SIV LS-mean (SE) LS-mean difference 95%CI P value	-2.4 (0.41)	-3.6 (0.42)	 1.2 (0.16, 2.32) 0.0247
	SIB LS-mean (SE) LS-mean difference 95%CI P value	-1.7 (0.79)	-6.6 (0.79)	 4.9 (2.80, 6.95) <.0001
	ADCS-CGIC n (%) Marked impr Moderate impr Minimal impr No change Minimal wors Moderate wors Marked wors	 3 (1.0) 11 (3.5) 63 (20.1) 107 (34.2) 76 (24.3) 44 (14.1) 9 (2.9)	 4 (1.3) 11 (3.5) 36 (11.4) 92 (29.2) 99 (31.4) 60 (19.0) 13 (4.1)	P value 0.0023
	NPI-12item LS-mean (SE) LS-mean difference 95%CI P value	-0.1 (0.84	1.5 (0.84)	 -1.6 (-3.84, 0.56) 0.1437

Primary efficacy results

Alzheimer's Disease Cooperative Study-Activity of Daily Living-Severe Impairment Version (ADCS-ADL-SIV)

Table 11-4 Summary statistics and treatment comparison in Alzheimer's Disease Cooperative Study-Activities of Daily Living-Severe Impairment Version (ADCS-ADL-SIV) total score (Modified Full Analysis set)

Visit / Statistics	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=338) SIB	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=338) Change from baseline	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N=335) SIB	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N=335) Change from baseline	13.3 mg vs. 4.6 mg
Baseline value (Up to Day 1)					
n	333		319		
Mean (SD)	29.7 (11.29)		29.1 (11.94)		
Median	31.0		31.0		
(Min, Max)	(0, 52)		(0, 52)		
Week 24 (Day 141 - [last dose date + 2 days])					
n	315	310	316	303	
Mean (SD)	27.4 (11.87)	-2.6 (6.82)	25.3 (12.22)	-3.6 (7.68)	
Median	29.0	-2.0	26.0	-3.0	
(Min, Max)	(0, 51)	(-26, 23)	(0, 53)	(-31, 18)	
p value[a]		<.0001		<.0001	
LS-mean (SE)[b]		-2.4 (0.41)		-3.6 (0.42)	
LS-mean difference					1.2
(95% CI)[b]					(0.16, 2.32)
p value[b]					0.0247

CI= confidence interval; LS= least squares; SE= standard error

Baseline was the last non-missing measurement on or prior to the day of first application of study medication.

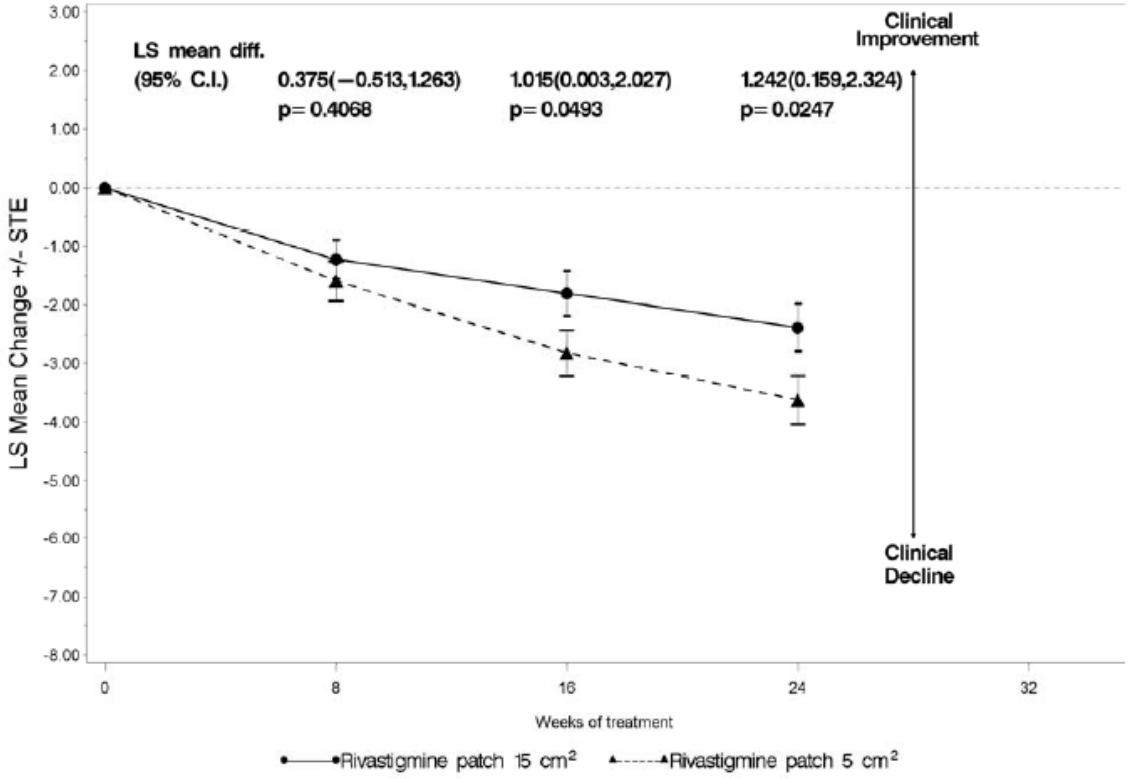
Missing data were imputed using the last-observation-carried-forward (LOCF) method.

[a]From a paired t-test for mean change from baseline within each treatment group

[b]From an analysis of covariance (ANCOVA) model with treatment and pooled center as factors, and baseline as a covariate

Decline in function, as measured by the mean change from DB-baseline in ADCS-ADL-SIV score, was less at each time point in the rivastigmine patch 15 cm2 group compared to the rivastigmine patch 5 cm2 group. For the MFAS-LOCF analysis, the between group differences were statistically significant in favour of the rivastigmine patch 15 cm2 group at Week 24, the co-primary endpoint (1.2 points; p=0.0247).

Figure 11-1 **Change from baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living - Severe Impairment Version (ADCS-ADL-SIV) total score at Week 8, Week 16, and Week 24 (Modified Full Analysis set)**



Severe Impairment Battery (SIB) total score

Table 11-5 Summary statistics and treatment comparison in Severe Impairment Battery total score (SIB) (Modified Full Analysis set)

Visit / Statistics	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=338) SIB	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=338) Change from baseline	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N=335) SIB	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N=335) Change from baseline	13.3 mg vs. 4.6 mg
Baseline value (Up to Day 1)					
n	336		334		
Mean (SD)	69.3 (21.54)		68.3 (22.79)		
Median	75.0		76.0		
(Min, Max)	(3, 99)		(4, 99)		
Week 24 (Day 141 - [last dose date + 2 days])					
n	315	313	317	316	
Mean (SD)	68.3 (24.36)	-1.6 (13.54)	62.5 (26.22)	-6.4 (14.01)	
Median	75.0.	0.0	67.0	-4.0	
(Min, Max)	(2, 100)	(-68, 82)	(0, 100)	(-52, 50)	
p value[a]		0.0424		<.0001	
LS-mean (SE)[b]		-1.7 (0.79)		-6.6 (0.79)	
LS-mean difference (95% CI)[b]					4.9 (2.80, 6.95)
p value[b]					<.0001

CI= confidence interval; LS= least squares; SD= standard deviation; SE= standard error

Baseline was the last non-missing measurement on or prior to the day of first application of study medication.

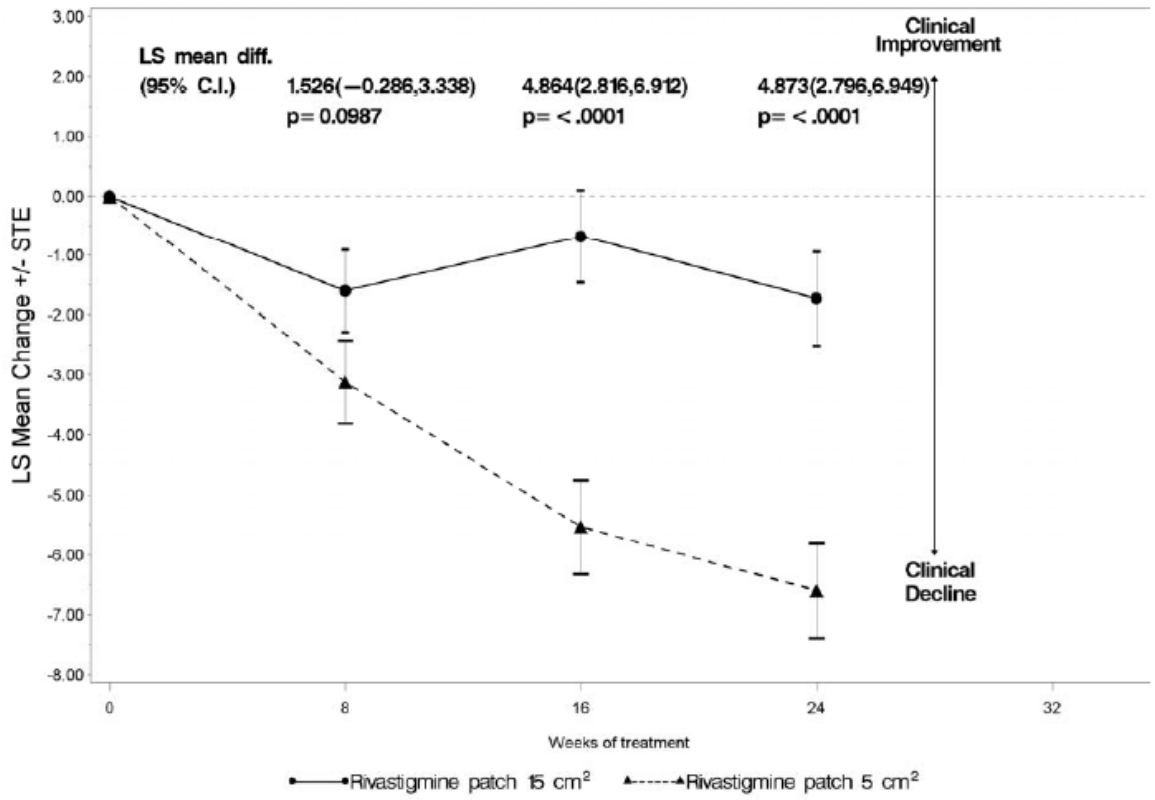
Missing data were imputed using the last-observation-carried-forward (LOCF) method.

[a]From a paired t-test for mean change from baseline within each treatment group

[b]From an analysis of covariance (ANCOVA) model with treatment and pooled center as factors, and baseline as a covariate

Decline in cognition, as measured by the mean change from DB-baseline in SIB score, was less at each time point in the rivastigmine patch 15 cm2 group compared to the rivastigmine patch 5 cm2 group. For the MFAS-last observation carried forward (LOCF) analysis, the between-treatment group differences were statistically significant in favour of the rivastigmine patch 15 cm2 group at Week 24, the co-primary endpoint (4.9 points; $p<0.0001$).

Figure 11-2 Change from baseline in Severe Impairment Battery (SIB) total score at Week 8, Week 16, and Week 24 (Modified Full Analysis set)



Sensitivity analyses were carried out in order to assess the robustness of the primary analysis results (longitudinal analysis based on a mixed-effects model with repeated measures (MMRM) and longitudinal analysis based on pattern mixture model (PMM). Results of these analyses are similar to those obtained with the primary LOCF analysis.

The applicant claims that a numerical difference, of 4.9 points on the SIB and 1.2 points on the ADCS-ADL-SIV, as measured in the whole population included in the pivotal US44 study, can be considered clinically meaningful based on published data; especially taking into account that in DUS44 the rivastigmine 15 cm2 patch was compared to a lower dose, and not placebo. The applicant refers to that a difference in total score of approximately 6 points in SIB and 2 points in the ADCS-ADLSIV was observed in a 28-week controlled study comparing memantine treatment versus placebo in a moderately severe AD population (Reisberg et al 2003). Another study comparing memantine versus placebo add-on to donepezil showed a difference of 3.4 points in SIB score and 1.6 points in ADCS-ADL-SIV at Week 24 (Tariot et al 2004); these two studies contributed to the approval of memantine.
However, the differences in the SIB and ADCS-ADL-SIV were smaller in the DUS44 study than in the memantine versus placebo study, which would be the study of most interest to compare with.

Responder analysis
As requested by the CHMP the Applicant further evaluated the clinical relevance of the results for the co-primary endpoints by a responder analysis, The responder analysis was performed using both the modified full analysis set and the randomized set.
ADCS-ADL-SIV responder analysis

For the modified full analysis set, the percentage of patients showing no change or improvement at Week 24 was 39% in the rivastigmine patch 15 cm2 group and 36% in the rivastigmine patch 5 cm2 group. The between-group difference was not statistically significant; similar results were seen at Week 24 for the randomized analysis set.

SIB responder analysis

For the modified full analysis set, the percentage of patients showing no change or improvement at Week 24 was 51.8% in the 15 cm2 group and 33.9% in the 5 cm2 group. The between-group difference was statistically significant (17.9 points p<.0001); similar results were seen at Week 24 for the randomized analysis set (12.4 points p=0.0008).

At the request of CHMP retrospective subgroup efficacy analyses for patients with a baseline MMSE score ≤9 and >9 were also performed.

Table 1-3 Summary statistics and treatment comparison ADCS-ADL-SIV total score by visit and treatment group, using baseline MMSE subgroup and its interaction with treatment as additional factors (Modified full analysis set)

	Rivastigmine patch 15 cm^2 (N=338)		Rivastigmine patch 5 cm^2 (N=335)
Baseline			
All patients			
n	333		319
Mean (SD)	29.7 (11.29)		29.1 (11.94)
MMSE ≤9			
n	164		161
Mean (SD)	26.6 (11.79)		24.8 (11.93)
MMSE >9			
n	169		158
Mean (SD)	32.7 (9.94)		33.6 (10.19)
Week 24			
All patients			
n	310		303
Mean (SD)	-2.6 (6.82)		-3.6 (7.68)
Change from baseline LS Mean (SE) [1]	-2.4 (0.40)		-3.6 (0.41)
LS Means difference (95% CI) [1]		1.2 (0.11, 2.25)	
p-value[1]		0.0303	
MMSE ≤9			
n	149		150
Mean (SD)	-3.9 (7.21)		-3.5 (7.67)
Change from baseline LS Mean (SE) [1]	-4.0 (0.59)		-4.4 (0.59)
LS Means difference (95% CI) [1]		0.4 (-1.17, 1.98)	
p-value[1]		0.6131	
MMSE >9			
n	161		153
Mean (SD)	-1.3 (6.21)		-3.8 (7.72)
Change from baseline LS Mean (SE) [1]	-0.8 (0.57)		-2.8 (0.59)
LS Means difference (95% CI) [1]		2.0 (0.44, 3.48)	
p-value[1]		0.0117	

Baseline was the last non-missing measurement on or prior to the day of first application of study medication.

Missing data were imputed using the last-observation-carried-forward (LOCF) method.

[1] From analysis of covariance (ANCOVA) model with treatment, pooled center, baseline MMSE subgroup, treatment-by-baseline MMSE subgroup as factors, and baseline ADCS-ADL-SIV as a covariate.

Change from baseline in SIB total score

Change from baseline in SIB total score was analyzed via a similar ANCOVA model as ADCS-ADL-SIV total score. Change from baseline in SIB total score was analyzed via an ANCOVA model with treatment, pooled center, baseline MMSE subgroup, treatment-by-baseline MMSE subgroup as factors, and baseline SIB as a covariate. Analysis of change from baseline in SIB total score by baseline MMSE score showed a statistically significant Least square (LS) Means difference in favour of the 15 cm2 rivastigmine patch for both the ≤9 and >9 MMSE subgroups at Week 24 (6.2 vs. 3.5 points, respectively); the difference being greater in the more severe subgroup (Table 1-2). The p-value for interaction at Week 24 was 0.1927, providing no evidence of a differential treatment effect by MMSE subgroup. Longitudinal analysis via a mixed-effects model with repeated measures (MMRM) model with treatment, pooled center, week, treatment-by-week, baseline MMSE group, treatment-by-baseline MMSE group, week-by-baseline MMSE group, treatment-by-week-by-baseline MMSE group as factors and baseline SIB as covariate (assuming un unstructured within-subject covariance matrix) was carried out to assess robustness of conclusions, and similar results were obtained.

Table 1-2 **Summary statistics and treatment comparison SIB total score by visit and treatment group, using baseline MMSE subgroup and its interaction with treatment as additional factors (Modified full analysis set)**

	Rivastigmine patch 15 cm^2 (N=338)		Rivastigmine patch 5 cm^2 (N=335)
Baseline			
All patients			
n	336		334
Mean (SD)	69.3 (21.54)		68.3 (22.79)
MMSE ≤9			
n	165		168
Mean (SD)	57.8 (22.33)		54.8 (22.24)
MMSE >9			
n	171		166
Mean (SD)	80.5 (13.44)		81.9 (13.18)
Week 24			
All patients			
n	313		316
Mean (SD)	-1.6 (13.54)		-6.4 (14.01)
Change from baseline LS Mean (SE) [1]	-1.9 (0.76)		-6.7 (0.77)
LS Means difference (95% CI) [1]		4.8 (2.85, 6.85)	
p-value[1]		<0.0001	
MMSE ≤9			
n	150		156
Mean (SD)	-3.7 (13.82)		-9.3 (14.76)
Change from baseline LS Mean (SE) [1]	-5.6 (1.16)		-11.8 (1.16)
LS Means difference (95% CI) [1]		6.2 (3.29, 9.18)	
p-value[1]		<0.0001	
MMSE >9			
n	163		160
Mean (SD)	0.4 (13.02)		-3.5 (12.66)
Change from baseline LS Mean (SE) [1]	1.8 (1.10)		-1.6 (1.14)
LS Means difference (95% CI) [1]		3.5 (0.62, 6.30)	
p-value[1]		0.0172	

Baseline was the last non-missing measurement on or prior to the day of first application of study medication.

Missing data were imputed using the last-observation-carried-forward (LOCF) method.

[1] From analysis of covariance (ANCOVA) model with treatment, pooled center, baseline MMSE subgroup, treatment-by-baseline MMSE subgroup as factors, and baseline SIB as a covariate.

Secondary efficacy results

Minimal or no changes in ADCS-CGIC ratings at Week 24 was observed in both groups. Changes in the 13.3 mg/24 h (15 cm2) patch group trended towards improvement, with more than half of patients showing either minimal improvement (20.1%) or no change (34.2%). A total of 24.3% of patients exhibited minimal worsening in this group. In the 4.6 mg/24 h (5 cm2) patch group, more than half of patients exhibited minimal worsening (31.4%) or no change (29.2%) from baseline to Week 24 while 11.4% showed minimal improvement.

The differences between treatment groups in the distributions of all ADCS-CGIC ratings were statistically significant in favour of the rivastigmine 15 cm2 patch group at Week 8 (p=0.0057), at Week 16 (p=0.0005) and at Week 24 (p=0.0023).

At Week 24, 58.8% in the rivastigmine 15 cm2 patch group showed either improvement (marked, moderate or minimal) or no change compared to 45.4% in the 5 cm2 group. The percentage of patients with no change or improvement in ADCS-CGIC in the rivastigmine 15 cm2 patch group were statistically significantly higher at each time point compared to the rivastigmine 5 cm2 patch group.

Table 11-6 Summary statistics and treatment comparison in Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) (Modified Full Analysis set)

	Rivastigmine patch		
	13.3 mg/24 h (15 cm^2)	4.6 mg/24 h (5 cm^2)	
Time point	(N=338)	(N= 335)	
Category	n (%)	n (%)	p-value[a]
Week 24 (Day 141 - [last dose date + 2 days])			0.0023
Marked improvement	3 (1.0)	4 (1.3)	
Moderate improvement	11 (3.5)	11 (3.5)	
Minimal improvement	63 (20.1)	36 (11.4)	
No change	107 (34.2)	92 (29.2)	
Minimal worsening	76 (24.3)	99 (31.4)	
Moderate worsening	44 (14.1)	60 (19.0)	
Marked worsening	9 (2.9)	13 (4.1)	

Note: Missing data were imputed using the last-observation-carried-forward (LOCF) method.

[a]From the Cochran-Mantel Haenszel Test (van Elteren test) with modified RIDIT (relative to an identified distribution integral transformation) scores (excluding missing values) adjusting for pooled center.

Neuropsychiatric Inventory-12 (NPI-12)

Changes in NPI-12 scores from baseline to Week 24 were observed in both groups.

Patients in the 13.3 mg/24 h (15 cm2) patch group showed a mean decrease of 0.4 points in NPI-12 scores during the study, while patients in the 4.6 mg/24 h (5 cm2) patch group showed an increase of 1.2 points. The LS means difference between treatment groups was numerically superior in the rivastigmine 15 cm2 patch group compared to 5 cm2 group. However, the difference was not statistically significant at week 24 (-1.6; p=0.1437).

Table 11-7 Summary statistics and treatment comparison in Neuropsychiatric Inventory (NPI-12) total score (Modified Full Analysis set)

Visit / Statistics	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=338) NPI-12	Rivastigmine patch 13.3 mg/24 h (15 cm^2) (N=338) Change from baseline	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N=335) NPI-12	Rivastigmine patch 4.6 mg/24 h (5 cm^2) (N=335) Change from baseline	13.3 mg vs. 4.6 mg
Baseline value (Up to Day 1)					
n	335		331		
Mean	17.3 (15.44)		16.8 (16.65)		
Median	13.0		13.0		
(Min, Max)	(0, 76)		(0, 114)		
Week 24 (Day 141 - [last dose date + 2 days])					
n	315	313	317	313	
Mean	16.7 (15.14)	-0.4 (14.01)	18.4 (18.81)	1.2 (16.79)	
Median	13.0	0.0	14.0	0.0	
(Min, Max)	(0, 70)	(-46, 46)	(0, 122)	(-80, 78)	
p-value value[a]		0.6409		0.2090	
LS-mean (SE)[b]		-0.1 (0.84)		1.5 (0.84)	
LS-mean difference					-1.6
(95% CI)[b]					(-3.84, 0.56)
p value[b]					0.1437

CI= confidence interval; LS= least squares; SE= standard error

Baseline was the last non-missing measurement on or prior to the day of first application of study medication.

Missing data were imputed using the last-observation-carried-forward (LOCF) method.

[a]From a paired t-test for mean change from baseline within each treatment group

[b]p-value from an analysis of covariance (ANCOVA) model with treatment and pooled center as factors, and baseline as a covariate

Long term efficacy data

Study ENA713DUS44E1 was an open-label, forced-titration 24-week extension to Study ENA713DUS44. After completing 24 weeks of double-blind treatment with either rivastigmine 13.3 mg/24 h/24 hours (15 cm2) or rivastigmine 4.6 mg/24 h/24 hours (5 cm2) patches, patients who entered the extension study were switched to a rivastigmine 9.5 mg/24 h/24 hours (10 cm2) patch for a 4-week dose-titration period. All patients were then titrated up to the 13.3 mg/24 h (15 cm2) patch and maintained for 20 weeks of treatment.

The primary objective of this open-label extension study was to provide further treatment with the 13.3 mg/24 h (15 cm2) rivastigmine patch and obtain further safety data with the patch in the treatment of patients with severe dementia of the Alzheimer's type who had previously completed the 24-week double-blind treatment study.

The secondary objectives were to obtain long-term efficacy data for the rivastigmine 13.3 mg/24 h (15 cm2) patch by assessments of:
• activities of daily living using the Alzheimer's Disease Cooperative Study-Activities of Daily Living-Severe Impairment Version (ADCS-ADL-SIV)
• cognition using the Severe Impairment Battery (SIB)
• global functioning using the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC).

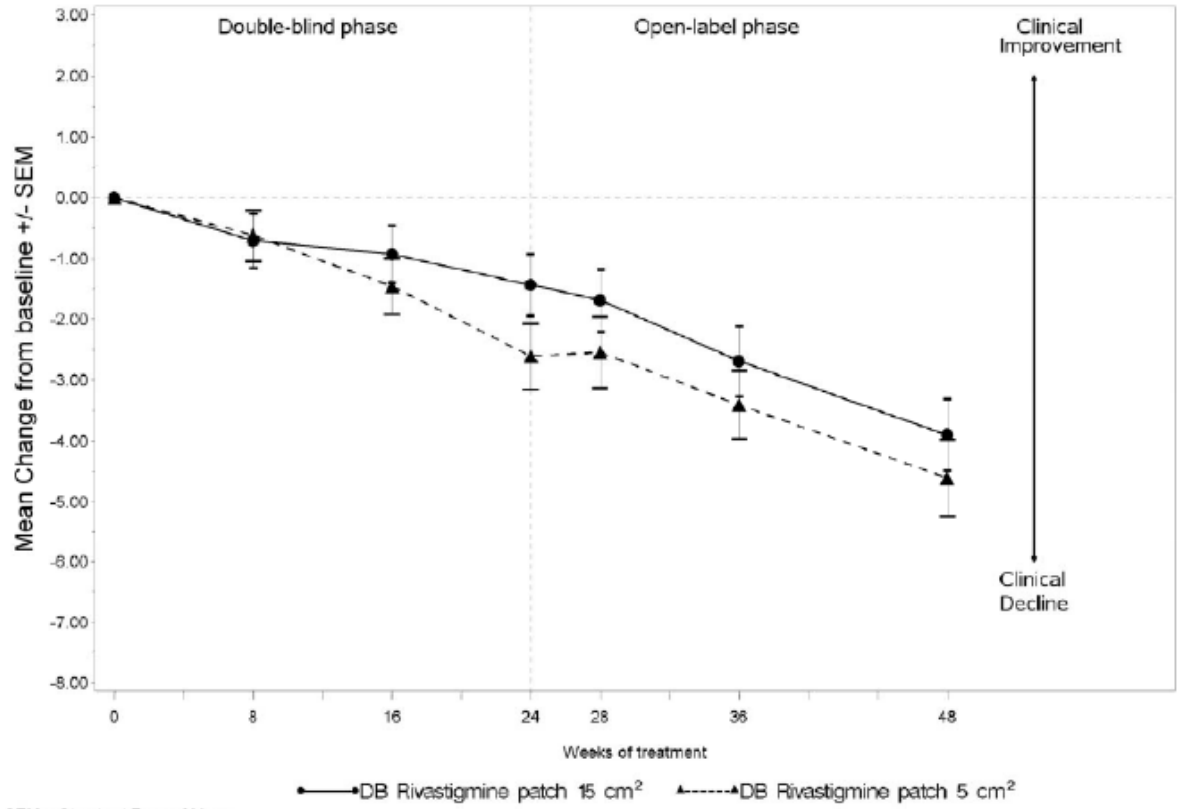
All 397 patients who completed 24 weeks of the double-blind study enrolled: 396 were included in the safety analyses and 381 in the efficacy analyses.

Outcomes

ADCS-ADL-SIV

For all patients, the mean decrease in ADCS-ADL-SIV score from double-blind baseline was 2 points at Week 24 (p<.0001) and 4.3 points at Week 48 (p<.0001).
ADCS-ADL-SIV total score showed less decline in function in patients who received rivastigmine 15 cm2 patch for the full 48 weeks compared to the patients who received 5 cm2 patch during the 24 weeks of Study DUS44 and 15 cm2 patch during the 24 weeks of Study DUS44E1 (-3.9 points and -4.6 points, respectively)..
Similar results were seen in the OC population (-3.9 points and -5.3 points, respectively).

Figure 11-1 Change in Alzheimer's Disease Cooperative Study-Activities of Daily Living-Severe Impairment Version (ADCS-ADL-SIV) total score (Modified full analysis set for open-label extension)-LOCF



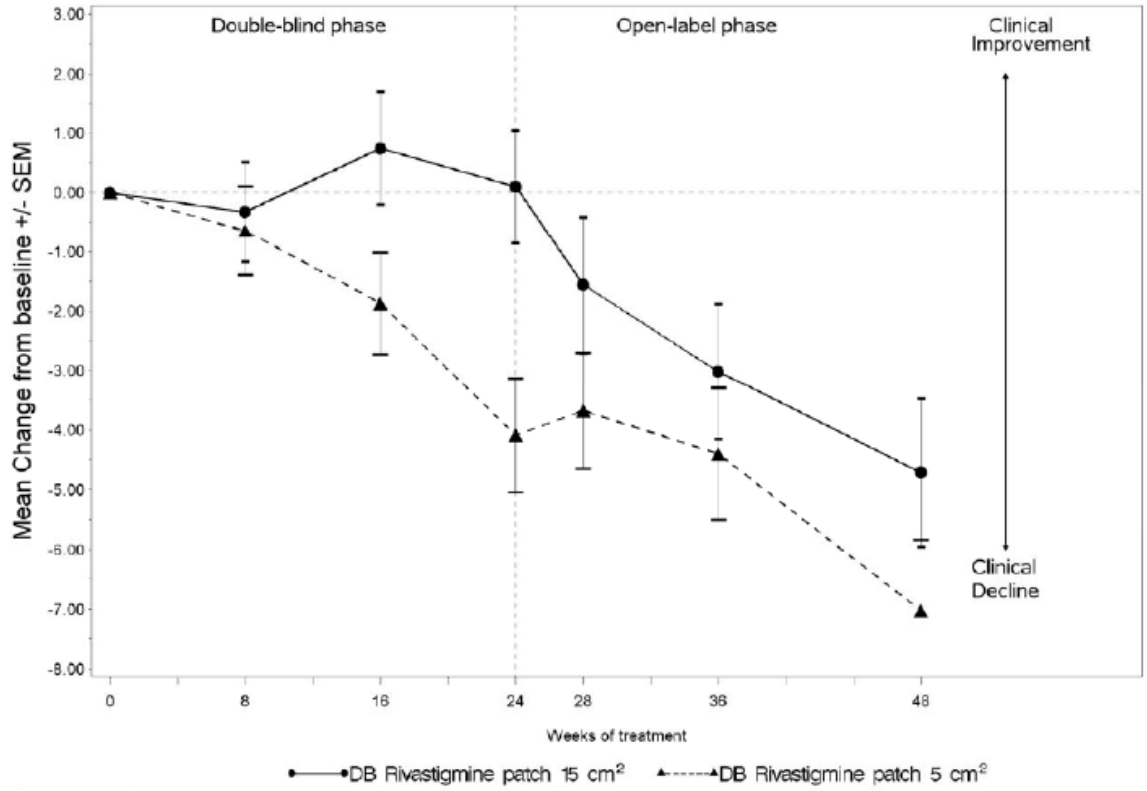
SEM = Standard Error of Mean
Source: Table 14.2-1.1

DB=double-blind; DB rivastigmine patch 15 cm^2=13.3 mg/24 h; DB rivastigmine patch 5 cm^2=4.6 mg/24 h

SIB

Mean change from baseline to the end of the open-label (OL) extension Study DUS44E1 (Week 48) in SIB total score showed less decline in cognition in patients who received rivastigmine 15 cm2 patch for the full 48 weeks compared to the patients who received 5 cm2 patch during the 24 weeks of Study DUS44 and 15 cm2 patch during the 24 weeks of Study DUS44E1 (-4.7 points and -7.0 points, respectively).
Similar results were seen in the OC population (-3.9 points and -6.4 points, respectively).

Figure 11-2 Change in Severe Impairment Battery (SIB) total score (Modified full analysis set for the open-label extension)-LOCF



SEM = Standard Error of Mean
Source: Table 14.2-2.1

DB=double-blind; DB rivastigmine patch 15 cm^2=13.3 mg/24 h; DB rivastigmine patch 5 cm^2=4.6 mg/24 h

ADCS-CGIC

Relative to double-blind baseline, the percentages of patients who improved, worsened, or showed no change in ADCS-CGIC ratings were similar between patients who continued and patients who switched to the 13.3 mg/24 h (15 cm2) patch. Approximately 16% of all patients showed improvement in mental/cognitive state, behaviour, and functioning as assessed by ADCS-CGIC ratings at Week 48 while more than half showed worsening and another quarter showed no change. Of the patients who continued on the 13.3 mg/24 h (15 cm2) patch, 15.7% showed minimal to marked improvement in ratings while 58.1% showed minimal to marked worsening. Of the patients who switched to the 13.3 mg/24 h (15 cm2) patch, 17.5% showed minimal to marked improvement and 56.4% showed minimal to marked worsening. No changes in ADCS-CGIC ratings were observed in 26.2% patients in both groups of patients.

Table 11-6 **Summary statistics and treatment comparison in Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) total score, LOCF approach (Modified full analysis set for open-label extension)**

Time point Category	Double-blind rivastigmine patch 15 cm^2 (N=186) n (%)	Double-blind rivastigmine patch 5 cm^2 (N=195) n (%)	Total (N=381) n (%)
Week 48 (Day 295 - [last dose date + 2 days])			
Marked improvement	2 (1.1)	5 (2.6)	7 (1.8)
Moderate improvement	12 (6.5)	7 (3.6)	19 (5.0)
Minimal improvement	15 (8.1)	22 (11.3)	37 (9.7)
No change	49 (26.3)	51 (26.2)	100 (26.2)
Minimal worsening	60 (32.3)	60 (30.8)	120 (31.5)
Moderate worsening	41 (22.0)	41 (21.0)	82 (21.5)
Marked worsening	7 (3.8)	9 (4.6)	16 (4.2)

Double-blind rivastigmine patch 15 cm^2=13.3 mg/24 h; Double-blind rivastigmine patch 5 cm^2=4.6 mg/24 h
Missing data were imputed using the last-observation-carried-forward (LOCF) method.

Supportive study

Study D2340

Study D2340 was a 48-week, DB, randomized, active-controlled, parallel group study, comparing the efficacy of the rivastigmine 15 cm2 and 10 cm2 patch in patients with mild to moderate AD (MMSE 10-24) demonstrating functional and cognitive decline after an initial 24-48 week open-label treatment phase at the maintenance dosage strength of rivastigmine 10 cm2 patch.

Supplementary post-hoc analysis are presented of the subset of severe AD patients from the double-blind phase of Study D2340. Out of 567 AD patients who had been randomized to the DB phase, 196 (34.6%) patients were classified with severe AD at DB-baseline (Randomized population, DB-baseline MMSE ≤12). Among these 196 patients, 193 had an MMSE score at DB-baseline ≥3 and ≤12 and 177 of them were included in the efficacy analysis (ITT-DB population DB-baseline MMSE ≥3 and ≤12).
The ITT-DB population includes all patients who were randomized, received at least one dose of study drug during the DB phase, and had at least one post-randomization assessment for both co-primary efficacy variables (ADAS-Cog, ADCS-Instrumental ADL) in the DB phase. This analysis was not powered to show statistical significance for the efficacy variables.

There were no meaningful differences observed between treatment groups in any of the baseline demographics and background characteristics. The MMSE were comparable between treatments groups (mean score of 9.0 in both, SCS Appendix 1-Table1.1-1, Table 1.1-2) and comparable to MMSE scores in study DUS44 (mean 8.8 in both treatment groups).

The proportion of severe patients (DB-baseline MMSE ≤12) discontinuing from the study was 26.2% for 15 cm2 and 36.6% for 10 cm2 patch [SCS Appendix 1-Table 1.1-3]. The Kaplan-Meier analysis of time to discontinuation due to AEs and time to discontinuation due to any reason suggest a slightly shorter time to event for the 10 cm2 patch compared to 15 cm2 patch.

Efficacy of the rivastigmine 15 cm2 patch versus rivastigmine 10 cm2 patch in the severe AD subpopulation (MMSE DB-baseline MMSE ≥3 and ≤12, n=177) was assessed by the change from DB randomization baseline to DB-week 48 in cognitive and functional abilities (ADAScog and Alzheimer's disease Cooperative Study-Instrumental Activity of Daily Living (ADCS-Instrumental ADL) subscales, respectively) in the ITT-DB population using LOCF.

The MMSE range of ≥3 and ≤12 at DB baseline was chosen to mirror the MMSE range used at baseline in Study DUS44.

Patients with severe AD treated with the rivastigmine 15 cm2 patch showed less decline (i.e. improved therapeutic benefit) in activities of daily living as measured by ADCS-Instrumental ADL subscale from baseline at all time points evaluated, when compared to rivastigmine 10 cm2 patch. For the ITT-DB(LOCF) analysis, the differences were statistically significant in favour of the rivastigmine 15 cm2 patch group at Week 16 (2.0 points; p=0.039), Week 24 (2.6 points; p=0.007), Week 32 (3.6 points; p<0.001) and Week 48 (3.0 points; p=0.006).

Patients with severe AD treated with the rivastigmine 15 cm2 patch showed less decline (i.e. improved therapeutic benefit) in cognition as measured by ADAS-cog from baseline at DB-Week 12, Week 24 and Week 48. At all time points evaluated, there was a numerical difference in favour of the rivastigmine 15 cm2 patch: Week 12 (-1.2 points; p=0.218), Week 24 (-1.0 points; p=0.370) and Week 48 (-0.8 points; p=0.482).

Discussion on clinical efficacy

Design and conduct of clinical studies

The application is mainly based on the pivotal study ENA713DUS44, that was a 24-week study designed to compare the efficacy and safety of rivastigmine 15 cm2 patch versus rivastigmine 5 cm2 patch in patients with a clinical diagnosis of severe dementia of the Alzheimer's type.
The length and the parallel group design of the study are appropriate. The inclusion and exclusion criteria ensured recruitment of consistent population representative of severe AD. The rational for the definition of severe AD as MMSE score of > 3 and < 12, inclusive, has been explained. However, for the applied indication of "severe AD", the efficacy and safety results in the patient population with MMSE score of ≤9 are of main importance, as the current indication is based on patient data from AD patients with MMSE score >9. The primary efficacy measures used to assess efficacy is in accordance with the guidelines for Alzheimer's disease. Nevertheless, in the more advanced forms of the disease, changes in cognitive performance may be less relevant to quantify. Hence choice of functional and global domains as primary endpoints could be more appropriate to establish clinically relevant symptomatic improvement in this severely impaired population. The clinical relevance of any difference has been analysed and discussed. It has been considered clinically meaningful based on published data. Nevertheless this is questionable. Secondary efficacy measures are considered acceptable.

A total of 463 (64.7%) of the 716 patients randomized completed the study: 229 (64.3%) in the rivastigmine 13.3 mg/24 h (15 cm2) patch group and 234 (65.0%) in the rivastigmine 4.6 mg/24 h (5 cm2) patch group. There were no statistically or clinically significant differences between treatment groups in any of the baseline or demographic characteristics, or background variables. However, it is noted that the 15 cm2 patch deliver a higher dose than the recommended dose (10 cm2 patch) in patients with mild to moderate severe AD.

The study was followed by the open label extension study ENA713DUS44E1 mainly to study long-term tolerability and safety.

As supportive evidence data are also adequately presented from a post-hoc analysis of the subset of severe AD patients from the double-blind phase of previously submitted Study D2340.

Efficacy data and additional analyses

In Study DUS44, cognitive decline as measured by the mean change from baseline in SIB total score was less at each time point in the rivastigmine 15 cm2 patch group than in the 5 cm2 patch group. The difference was statistically significant in favour of the rivastigmine 15 cm2 patch at Week 24, the primary end point (4.9 points, p<0.0001).

Decline in function as measured by the mean change from baseline in ADCS-ADL-SIV total score, was less at each time point in the rivastigmine 15 cm2 patch group than in the 5 cm2 patch group. The difference was statistically significant in favour of the rivastigmine 15 cm2 patch at Week 24, the co-primary end point (1.2 points, p=0.0247).

The difference of treatment group in cognitive and in function response was maintained throughout the 24 week period.

In Study DUS44E1, patients randomized to rivastigmine 5 cm2 patch in the DB phase seem to have benefited from switching to rivastigmine 15 cm2 in the OL extension phase. However, they

did not reach the same efficacy level as those randomized to 15 cm2 in the DB phase. Nevertheless, due to the open-label nature of the study the interpretability of efficacy data is limited.

In Study 2340 the 15 cm2 treatment group showed statistical and numerical, respectively, less decline compared to the 10 cm2 group as measured by both the ADCS-Instrumental ADL subscale and the ADAS-cog.

Conclusions on clinical efficacy

Taken together, the efficacy results in the defined population support an effect of the higher dose 15 cm2 compared to 5 cm2. The claim by the Applicant that the difference on the SIB and on the ADCS-ADL-SIV between the treatments groups in the pivotal US44 study can be considered clinically meaningful, based on published data, is questionable.
Only one of the primary endpoints (SIB total score) showed a statistical significant difference between the two dose groups in the patients with a baseline MMSE score of ≤ 9 points.

For the responder analysis of the primary variable SIB the between treatment group differences was statistically significant but not for the ADCS-ADL-SIV, the other primary end-point. The applicant had not performed the responder analyses for the ≤9 and >9 MMSE subgroups

Clinical safety

The objective of the safety analysis made by the Applicant was to assess the safety and tolerability of the 13.3 mg/24 h (15 cm2) rivastigmine patch formulation.

The safety results from the pivotal (Study DUS44) and its open-label extension (Study DUS44E1) are the primary datasets for the assessment of safety.

Supplementary post-hoc analyses for the severe subpopulation (patients with MMSE ≤ 12) of Study D2340 (pivotal study to support the registration of rivastigmine patch 13.3 mg/24h dosage strength in mild to moderate AD) are also presented.

The results of safety data are presented according to the following groupings:

Dataset A:
• Study DUS44: Week 0 to Week 24 DB safety data

Dataset B:
• Study DUS44E1 24-week open-label extension safety data

Dataset C:
• Study DUS44/Study DUS44E1 combined 48-week safety data

Dataset D:
• Study D2340 (supplementary post-hoc subgroup analysis in severe patients): 48-week DB safety data

Table 1-5 Population groupings for safety assessment

Database	Studies	Number of patients (safety population)	Safety topics
Dataset A	DUS44 (24-week, double-blind safety data)	Rivastigmine 15 cm^2 : 355 Rivastigmine 5 cm^2: 359 (total 714)	All AEs, AEs by severity, AEs leading to discontinuation, Serious adverse events (SAEs), deaths, potential and identified risks.
Dataset B	DUS44E1 (24 week open label extension study)	Rivastigmine 15 cm^2: 396	All AEs, AEs by severity, AEs leading to discontinuation, SAEs, deaths, potential and identified risks.
Dataset C	DUS44+DUS44E1 (48-week safety data)	Rivastigmine 15 cm^2 : 396	All AEs, AEs by severity, AEs leading to discontinuation, SAEs, deaths, potential and identified risks.
Dataset D	D2340 (48-week safety data)	Severe subpopulation Rivastigmine 15 cm^2: 103 Rivastigmine 10 cm^2 patch: 92 (total 195)	All AEs, AEs by severity, AEs leading to discontinuation, SAEs, deaths
	D2340 (first 24 weeks and > 24 weeks safety data)	First 24 weeks : Rivastigmine 15 cm^2: 103 First 24 weeks: Rivastigmine 10 cm^2 patch: 92 (total 195) >24 weeks : Rivastigmine 15 cm^2: 87 >24 weeks: Rivastigmine 10 cm^2 patch: 76 (total 163)	Common AEs

For DUS44, all adverse events with start date on or after the date of first study medication were included.

For DUS44E1, all adverse events occurring on or after the date of first open-label study medication were included.

For DUS44 and DUS44E1 study phases combined, all adverse events with start date on or after the date of first double-blind study medication were included.

For D2340 first 24 weeks of the double-blind phase, all AEs with onset on or after the first dose of study medication in the double-blind phase and within the first 24 weeks of the same phase are presented in the summary tables. For the >24 weeks period of the D2340 double-blind phase, all AEs with onset on or after the first dose of study medication after Week 24 of the double-blind phase for the subjects that were still in the study after Week 24 of that phase are presented in separate summaries. For both tabulations, only patients with DB-baseline MMSE <=12 in the DB-safety population are considered.

Patient exposure

In the 24-week DB phase of Study DUS44, the mean and median durations of exposure to study drug were similar in the rivastigmine 15 cm2 and 5 cm2 patch treatment groups.

Table 12-2 Duration (weeks) of exposure to study medication (Safety set)

	Rivastigmine patch		
	13.3 mg/24 h (15 cm^2)	4.6 mg/24 h (5 cm^2)	Total
	(N=355)	(N= 359)	(N= 714)
Duration of exposure (weeks)	**n (%)**	**n (%)**	**n (%)**
Any Exposure	355 (100.0)	359 (100.0)	714 (100.0)
At least 1 week	350 (98.6)	355 (98.9)	705 (98.7)
At least 2 weeks	346 (97.5)	348 (96.9)	694 (97.2)
At least 3 weeks	338 (95.2)	340 (94.7)	678 (95.0)
At least 4 weeks	336 (94.6)	334 (93.0)	670 (93.8)
At least 8 weeks	310 (87.3)	311 (86.6)	621 (87.0)
At least 16 weeks	255 (71.8)	277 (77.2)	532 (74.5)
At least 24 weeks	199 (56.1)	198 (55.2)	397 (55.6)
Descriptive Statistics (weeks)			
n	355	358	713
Mean	19.64	20.07	19.85
SD	7.893	7.621	7.755
Median	24.00	24.00	24.00
(Min, Max)	(0.3, 36.9)	(0.4, 28.9)	(0.3, 36.9)

SD= standard deviation

Duration of exposure (weeks) =(the last study medication date - first study medication date +1)/7.

In the 24-week Study DUS44E1, the mean and median durations of exposure to study drug were similar in the rivastigmine 15 cm2/15 cm2 and 5 cm2/15 cm2 patch treatment groups.

Table 1-7 Duration of exposure (Weeks) to study drug, by treatment group (Study DUS44E1- Safety population)

	Rivastigmine 15 cm^2/15 cm^2 [(a)]	Rivastigmine 5 cm^2 /15 cm^2 [(b)]	Total
	(N=197)	(N= 199)	(N= 396)
Duration of exposure (weeks)			
n	197	199	396
Mean	21.66	21.17	21.42
SD	6.883	7.480	7.185
Median	24.00	24.00	24.00
(Min, Max)	(0.0, 34.0)	(0.0, 30.0)	(0.0, 34.0)

[(a)] Patients treated with the rivastigmine15 cm^2 patch during DB core Study DUS44 and during the open-label extension.

[(b)] Patients treated with the rivastigmine 5 cm^2 patch during DB core Study DUS44 and the rivastigmine15 cm^2 patch during the open-label extension.

Note: Duration of exposure (weeks) = (the last study medication date - first study medication date +1)/7.

Adverse events

Dataset A: Study DUS44, 24-week DB safety data

During the 24 weeks the overall incidence rate of AEs was similar in both treatment groups (15 cm2: 74.6%; 5 cm2: 73.3%).

The percentages of patients with events in the General disorders and administration site conditions, Infections and Infestation and Nervous system disorders SOCs were similar in both treatment groups. The percentages of patients with events in the Psychiatric disorders and Gastrointestinal disorders SOCs were approximately 4% higher in the rivastigmine 15 cm2 patch group compared to the rivastigmine 5 cm2 patch group. In the Metabolism and nutrition disorders and

Investigations SOCs the percentages of patients with AEs were also more frequent in the rivastigmine 15 cm2 group than in the 5 cm2 group (11.8% vs. 8.4%, respectively and 12.4% vs. 8.4%, respectively); otherwise there were no meaningful differences between treatment groups.

Primary system organ class	Rivastigmine 15 cm^2 patch N = 355 n (%)	Rivastigmine 5 cm^2 patch N = 359 n (%)	Total N = 714 n (%)
Any primary system organ class	265 (74.6)	263 (73.3)	528 (73.9)
General disorders and administration site conditions	117 (33.0)	116 (32.3)	233 (32.6)
Psychiatric disorders	111 (31.3)	97 (27.0)	208 (29.1)
Gastrointestinal disorders	70 (19.7)	56 (15.6)	126 (17.6)
Infections and infestations	62 (17.5)	67 (18.7)	129 (18.1)
Nervous system disorders	57 (16.1)	59 (16.4)	116 (16.2)
Injury, poisoning and procedural complications	44 (12.4)	47 (13.1)	91 (12.7)
Investigations	44 (12.4)	30 (8.4)	74 (10.4)
Metabolism and nutrition disorders	42 (11.8)	30 (8.4)	72 (10.1)
Skin and subcutaneous tissue disorders	31 (8.7)	25 (7.0)	56 (7.8)
Renal and urinary disorders	29 (8.2)	28 (7.8)	57 (8.0)
Respiratory, thoracic and mediastinal disorders	24 (6.8)	21 (5.8)	45 (6.3)
Musculoskeletal and connective tissue disorders	23 (6.5)	21 (5.8)	44 (6.2)
Vascular disorders	23 (6.5)	20 (5.6)	43 (6.0)
Cardiac disorders	13 (3.7)	20 (5.6)	33 (4.6)
Blood and lymphatic system disorders	7 (2.0)	9 (2.5)	16 (2.2)
Eye disorders	5 (1.4)	2 (0.6)	7 (1.0)
Ear and labyrinth disorders	4 (1.1)	1 (0.3)	5 (0.7)
Hepatobiliary disorders	4 (1.1)	2 (0.6)	6 (0.8)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	4 (1.1)	4 (1.1)	8 (1.1)
Reproductive system and breast disorders	2 (0.6)	1 (0.3)	3 (0.4)
Surgical and medical procedures	2 (0.6)	3 (0.8)	5 (0.7)
Immune system disorders	1 (0.3)	0	1 (0.1)
Endocrine disorders	0	4 (1.1)	4 (0.6)

System Organ Classes are presented in descending frequency in the 15 cm^2 column
A patient with multiple occurrences of an adverse event was counted only once in the AE category.
A patient with multiple adverse events within a system organ class was counted only once in the total row.
Only adverse events started on or after the date of first application of study medication were included.
Source: [Study DUS44-PT Table 14.3.1-1.1]

Most of the reported AEs were expected. Of the most frequent events, the following were observed more often in the rivastigmine 15 cm2 patch group compared to the 5 cm2 group: application site erythema, (13.2% vs. 11.7%, respectively), fall (7.6% vs. 5.8%, respectively), insomnia (7.0% vs. 4.2%, respectively), vomiting (7.0% vs. 2.5%, respectively), diarrhoea, (6.5% vs. 5.3%, respectively), weight decreased (6.5% vs. 3.1%, respectively), nausea (6.2% vs. 2.8%, respectively), decreased appetite (4.8% vs. 1.4%, respectively), somnolence (3.4% vs. 2.5%, respectively), dehydration (3.1% vs. 2.2%, respectively), dizziness (3.1% vs. 1.4%, respectively), laceration (2.5% vs. 1.4%, respectively), fatigue (2.5% vs. 0.8%, respectively), asthenia (2.3% vs. 0.8%, respectively) and rash (2.3% vs. 0.8%, respectively).

Common AEs of special interest reported in less than 5% of patients with a difference of at least 2% between the rivastigmine 15 cm2 and 5 cm2 groups included decreased appetite 4.8% vs. 1.4%.

Preferred term	Rivastigmine 15 cm^2 patch N = 355 n (%)	Rivastigmine 5 cm^2 patch N = 359 n (%)	Total N = 714 n (%)
Total number of patients with AE(s)	265 (74.6)	263 (73.3)	528 (73.9)
Application site erythema	47 (13.2)	42 (11.7)	89 (12.5)
Agitation	41 (11.5)	51 (14.2)	92 (12.9)
Urinary tract infection	29 (8.2)	34 (9.5)	63 (8.8)
Application site dermatitis	27 (7.6)	33 (9.2)	60 (8.4)
Fall	27 (7.6)	21 (5.8)	48 (6.7)
Insomnia	25 (7.0)	15 (4.2)	40 (5.6)
Vomiting	25 (7.0)	9 (2.5)	34 (4.8)
Diarrhoea	23 (6.5)	19 (5.3)	42 (5.9)
Weight decreased	23 (6.5)	11 (3.1)	34 (4.8)
Nausea	22 (6.2)	10 (2.8)	32 (4.5)
Depression	17 (4.8)	15 (4.2)	32 (4.5)
Decreased appetite	17 (4.8)	5 (1.4)	22 (3.1)
Anxiety	16 (4.5)	16 (4.5)	32 (4.5)
Hypertension	13 (3.7)	9 (2.5)	22 (3.1)
Application site pruritus	13 (3.7)	8 (2.2)	21 (2.9)
Confusional state	12 (3.4)	13 (3.6)	25 (3.5)
Somnolence	12 (3.4)	9 (2.5)	21 (2.9)
Constipation	11 (3.1)	12 (3.3)	23 (3.2)
Urinary incontinence	11 (3.1)	10 (2.8)	21 (2.9)
Application site irritation	11 (3.1)	9 (2.5)	20 (2.8)
Dehydration	11 (3.1)	8 (2.2)	19 (2.7)
Dizziness	11 (3.1)	5 (1.4)	16 (2.2)
Upper respiratory tract infection	9 (2.5)	9 (2.5)	18 (2.5)
Laceration	9 (2.5)	5 (1.4)	14 (2.0)
Fatigue	9 (2.5)	3 (0.8)	12 (1.7)
Oedema peripheral	8 (2.3)	12 (3.3)	20 (2.8)
Hypokalaemia	8 (2.3)	6 (1.7)	14 (2.0)
Asthenia	8 (2.3)	3 (0.8)	11 (1.5)
Rash	8 (2.3)	3 (0.8)	11 (1.5)
Hallucination	7 (2.0)	16 (4.5)	23 (3.2)
Abnormal behaviour	7 (2.0)	10 (2.8)	17 (2.4)
Contusion	7 (2.0)	8 (2.2)	15 (2.1)
Syncope	7 (2.0)	8 (2.2)	15 (2.1)
Hypotension	4 (1.1)	8 (2.2)	12 (1.7)

Preferred terms are sorted by descending frequency in the rivastigmine 15 cm^2 treatment group.
A patient with multiple occurrences of an adverse event was counted only once in the AE category.
Only adverse events occurring on or after the day of first application of study medication were included.
Source: [Study DUS44-PT Table 14.3.1-1.6]

The incidence of severe AEs was slightly higher in the rivastigmine 15 cm2 patch group. Differences between the 15 cm2 and the 5 cm2 patch group with a higher frequency of severe AEs in the 15cm2 group were mainly noted in the Gastrointestinal AEs and metabolism and nutrition disorders. Of the gastrointestinal AEs reported as severe, nausea (n=3), diarrhoea (n=2), and vomiting (n=2) were the most common events in the 13.3 mg/24 h (15 cm2) patch group while constipation (n=2) was the most common gastrointestinal event in the 4.6 mg/24 h (5 cm2) patch group. All of the severe events of metabolism and nutrition disorders were experienced by patients in the 15 cm2 patch group. Two patients experienced in this group severe decreased appetite and 2 experienced severe dehydration (n=3).

Table 2-5 Number (%) of patients with AEs by maximum severity, treatment group and study (24-week Study DUS44 – Safety population)

	Rivastigmine 15 cm^2 patch N = 355 n (%)	Rivastigmine 5 cm^2 patch N = 359 n (%)	Total N = 714 n (%)
Patients with mild* AEs	106 (29.9)	113 (31.5)	219 (30.7)
Patients with moderate* AEs	115 (32.4)	114 (31.8)	229 (32.1)
Patients with severe* AEs	44 (12.4)	36 (10.0)	80 (11.2)

* maximum severity within a patient

Any AE starting on or after the first dose in DB phase is included in this table.

A patient with multiple severity ratings for an AE while on a treatment, is only counted under the maximum rating

Application site skin irritation

Evaluation of application site skin irritation was based on inspection by the investigator of the skin at the sites of application with regard to intensity of the signs and symptoms of intolerance (i.e. erythema, oedema, scaling, fissures, pruritus, pain, stinging and/or burning).

The skin irritation assessment was to be completed at Weeks 4, 8, 16 and 24. Severity was rated on a 4-point scale ranging from very mild to severe with a score of 0 for no or negative skin irritation.
After Week 4 (the study involved a double-dummy design) the assessment of skin irritation was based on the application of 2 patches simultaneously on each patient, allowing for potentially higher incidence rates of skin reactions compared to once daily application in clinical practice.

Approximately 91% of patients in both treatment groups were assessed as ‘no’ or ‘negative’ on the skin irritation scale for erytheme at Week 4. After Week 4, there was an increase in the percentage of patients reporting erythema in both treatment groups.

The majority of these reactions were rated as very slight, mild or moderate. In the 15 cm2 patch group only 1 (0.3%) was rated severe at Week 8, 4 (1.6%) at Week 16 and 2 (0.9%) at Week 24; in the 5 cm2 patch group only 2 (0.6%) patients were rated as severe at Week 4, 4 (1.3%) at Week 8, 3 (1.1%) at Week 16 and 3 (1.3%) at Week 24.

Over 95% of patients in both treatment groups reported ‘no’ or ‘negative’ at all time points for the other items (i.e. oedema, scaling, fissures, pruritus pain, stinging and/or burning). All skin reactions were assessed at very slight, mild or moderate, except for 2 (0.9%) patients in the 15 cm2 patch group and 1 (0.4%) patients in the 5 cm2 group at Week 24 with severe pruritus.

Table 2-3 **Number (%) of patients reporting 'no' or 'negative' on the Investigator skin irritation scale by item, time point and treatment group (Study DUS44 – Safety population)**

Skin irritation scale item	Rivastigmine15 cm^2 patch (N=355) n (%)*	Rivastigmine 5 cm^2 patch (N= 359) n (%)*	Total (N= 714) n (%)*
Erythema ('No')			
Week 4	304 (91.3)	307 (91.6)	611 (91.5)
Week 8	265 (85.8)	280 (89.7)	545 (87.8)
Week 16	205 (79.5)	240 (86.6)	445 (83.2)
Week 24	190 (82.3)	201 (86.6)	391 (84.4)
Edema ('No')			
Week 4	329 (98.8)	332 (99.1)	661 (99.0)
Week 8	304 (98.7)	308 (98.7)	612 (98.7)
Week 16	250 (97.3)	271 (97.8)	521 (97.6)
Week 24	222 (96.5)	226 (97.4)	448 (97.0)
Scaling ('No')			
Week 4	330 (99.1)	330 (98.5)	660 (98.8)
Week 8	304 (98.7)	307 (98.4)	611 (98.5)
Week 16	245 (95.3)	271 (97.8)	516 (96.6)
Week 24	223 (97.0)	229 (98.7)	452 (97.8)
Fissures ('No')			
Week 4	333 (100.0)	334 (99.7)	667 (99.9)
Week 8	308 (100.0)	312 (100.0)	620 (100.0)
Week 16	257 (100.0)	276 (99.6)	533 (99.8)
Week 24	229 (99.6)	232 (100.0)	461 (99.8)
Pruritus (Negative)			
Week 4	328 (98.5)	331 (98.8)	659 (98.7)
Week 8	302 (98.1)	302 (96.8)	604 (97.4)
Week 16	247 (96.1)	269 (97.1)	516 (96.6)
Week 24	219 (95.2)	223 (96.1)	442 (95.7)
Pain, stinging and/or burning ('No')			
Week 4	332 (99.7)	333 (99.4)	665 (99.6)
Week 8	308 (100.0)	312 (100.0)	620 (100.0)
Week 16	254 (98.8)	274 (98.9)	528 (98.9)
Week 24	227 (98.7)	229 (98.7)	456 (98.7)

* percentage calculated with respect to number of patients with non-missing values for each symptom.

The worst skin irritation within each window were used for calculation

Subjects reported no skin irritation in the Case Reort Form (CRF) were classified as 'No' or 'Negative' response in each symptom.

Very few discontinuations due to application site reactions were reported in both groups.

Table 2-4 Application site AEs leading to discontinuation by preferred term and treatment group (Study DUS44 – Safety population)

Application site AEs	Rivastigmine15 cm^2 patch (N=355) n (%)	Rivastigmine 5 cm^2 patch (N= 359) n (%)	Total (N= 714) n (%)
Application site erythema	3 (0.8)	2 (0.6)	5 (0.7)
Application site pruritus	2 (0.6)	3 (0.8)	5 (0.7)
Application site dermatitis	1 (0.3)	2 (0.6)	3 (0.4)
Application site irritation	1 (0.3)	2 (0.6)	3 (0.4)
Application site rash	1 (0.3)	1 (0.3)	2 (0.3)
Application site pain	0	1 (0.3)	1 (0.1)
Application site vesicles	1 (0.3)	0	1 (0.1)

Any AE starting on or after the first dose of DB phase is included in this table.

Preferred terms are sorted in descending frequency of rivastigmine 15 cm^2.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

A patient with multiple AEs within a primary system organ class is counted only once in a total row.

Dataset B: Study DUS44E1 24-week open-label extension study safety data

The overall incidence rate of AEs was similar in both treatment groups during the 24 weeks of the study (57.9% in the group rivastigmine 15 cm2/15 cm2 versus 59.8 in the group rivastigmine 5 cm2/15cm2).

The most frequently affected SOCs during the extension study were Infections and infestations, Psychiatric disorders, Gastrointestinal disorders and Nervous system disorders.

The percentages of patients with Psychiatric disorders, Gastrointestinal disorders, Respiratory, thoracic and mediastinal disorders, Renal and urinary disorders were lower in the group treated with the rivastigmine 15 cm2 patch during the core study (rivastigmine 15 cm2/15 cm2 group) than in the group treated with the rivastigmine 5 cm2 patch during the core study (rivastigmine 5 cm2/15 cm2 group).

Percentages of patients with Skin and subcutaneous tissue disorders, Injury and poisoning and procedural complications and Musculoskeletal and connective tissue disorders, Vascular disorders and Eye disorders AEs were higher for the rivastigmine 15 cm2/15 cm2 group than in the 5 cm2/15 cm2 group. In the remaining SOCs, the percentages of patients reporting AEs were similar for both treatment groups.

Table 2-6 AEs by primary system organ class and treatment group (24-week Study DUS44E1- Safety population for open-label extension)

Primary system organ class	Rivastigmine 15 cm^2/15 cm^2 [a] N = 197 n (%)	Rivastigmine 5 cm^2 /15 cm^2 [b] N = 199 n (%)	Total N = 396 n (%)
Any primary system organ class	114 (57.9)	119 (59.8)	233 (58.8)
Infections and infestations	37 (18.8)	36 (18.1)	73 (18.4)
Nervous system disorders	28 (14.2)	27 (13.6)	55 (13.9)
Psychiatric disorders	28 (14.2)	38 (19.1)	66 (16.7)
Gastrointestinal disorders	26 (13.2)	33 (16.6)	59 (14.9)
Investigations	26 (13.2)	26 (13.1)	52 (13.1)
General disorders and administration site conditions	21 (10.7)	23 (11.6)	44 (11.1)
Injury, poisoning and procedural complications	20 (10.2)	17 (8.5)	37 (9.3)
Metabolism and nutrition disorders	14 (7.1)	12 (6.0)	26 (6.6)
Musculoskeletal and connective tissue disorders	14 (7.1)	7 (3.5)	21 (5.3)
Skin and subcutaneous tissue disorders	11 (5.6)	4 (2.0)	15 (3.8)
Vascular disorders	11 (5.6)	8 (4.0)	19 (4.8)
Cardiac disorders	9 (4.6)	9 (4.5)	18 (4.5)
Respiratory, thoracic and mediastinal disorders	8 (4.1)	12 (6.0)	20 (5.1)
Eye disorders	4 (2.0)	2 (1.0)	6 (1.5)
Renal and urinary disorders	4 (2.0)	11 (5.5)	15 (3.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.5)	3 (1.5)	6 (1.5)
Blood and lymphatic system disorders	2 (1.0)	2 (1.0)	4 (1.0)
Reproductive system and breast disorders	2 (1.0)	2 (1.0)	4 (1.0)
Ear and labyrinth disorders	1 (0.5)	0	1 (0.3)
Hepatobiliary disorders	1 (0.5)	0	1 (0.3)
Social circumstances	1 (0.5)	0 (0.0)	1 (0.3)
Congenital, familial and genetic disorders	0	1 (0.5)	1 (0.3)
Endocrine disorders	0	1 (0.5)	1 (0.3)

[a] Patients treated with the rivastigmine15 cm^2 patch during DB core Study DUS44 and during the open-label extension.

[b] Patients treated with the rivastigmine 5 cm^2 patch during DB core Study DUS44 and the rivastigmine15 cm^2 patch during the open-label extension.

System Organ Classes are presented in descending frequency in the rivastigmine 15 cm^2/15 cm^2 column
A patient with multiple occurrences of an adverse event was counted only once in the AE category.
A patient with multiple adverse events within a system organ class was counted only once in the total row.
Only adverse events started on or after the date of first application of study medication were included.

Frequent AEs

No unexpected AEs were reported. Of the commonly observed AEs (at least 2% in either treatment group), the most frequent events (>5%) for patients who were treated with the rivastigmine 15 cm2 patch during the core and extension studies (15 cm2/15 cm2 group) were urinary tract infection and weight decreased; these AEs were observed in similar percentages of patients in the 5 cm2/15 cm2 group. Fall was reported in a lower percentage of patients in the 15 cm2/15 cm2 group than 5 cm2/15 cm2 group. The incidence of nausea, vomiting and diarrhoea were notably low in those patients who had been treated with the 15 cm2 patch during the core study and were reported more frequently in those treated with the 5 cm2 rivastigmine patch during the core study.

Table 2-7 **Number (%) of patients with AEs (at least 2% in either treatment group) by preferred term and treatment group (24-week Study DUS44E1- Safety population for open-label extension).**

Preferred term	Rivastigmine 15 cm^2/15 cm^2 [a] N = 197 n (%)	Rivastigmine 5 cm^2 /15 cm^2 [b] N = 199 n (%)	Total N = 396 n (%)
Total number of patients with AE(s)	114 (57.9)	119 (59.8)	233 (58.8)
Urinary tract infection	22 (11.2)	21 (10.6)	43 (10.9)
Weight decreased	15 (7.6)	15 (7.5)	30 (7.6)
Fall	9 (4.6)	12 (6.0)	21 (5.3)
Agitation	9 (4.6)	11 (5.5)	20 (5.1)
Vomiting	6 (3.0)	16 (8.0)	22 (5.6)
Diarrhoea	5 (2.5)	10 (5.0)	15 (3.8)
Syncope	5 (2.5)	3 (1.5)	8 (2.0)
Insomnia	4 (2.0)	8 (4.0)	12 (3.0)
Application site dermatitis	4 (2.0)	4 (2.0)	8 (2.0)
Decreased appetite	4 (2.0)	4 (2.0)	8 (2.0)
Dehydration	4 (2.0)	4 (2.0)	8 (2.0)
Hypertension	4 (2.0)	3 (1.5)	7 (1.8)
Muscular weakness	4 (2.0)	0	4 (1.0)
Nausea	3 (1.5)	8 (4.0)	11 (2.8)
Contusion	3 (1.5)	5 (2.5)	8 (2.0)
Abdominal pain	3 (1.5)	4 (2.0)	7 (1.8)
Application site erythema	3 (1.5)	4 (2.0)	7 (1.8)
Anxiety	2 (1.0)	5 (2.5)	7 (1.8)
Depression	2 (1.0)	5 (2.5)	7 (1.8)
Pneumonia	2 (1.0)	4 (2.0)	6 (1.5)
Somnolence	2 (1.0)	4 (2.0)	6 (1.5)
Urinary incontinence	2 (1.0)	4 (2.0)	6 (1.5)
Mental status changes	1 (0.5)	5 (2.5)	6 (1.5)
Confusional state	1 (0.5)	4 (2.0)	5 (1.3)
Convulsion	1 (0.5)	4 (2.0)	5 (1.3)
Delusion	1 (0.5)	4 (2.0)	5 (1.3)
Dizziness	1 (0.5)	4 (2.0)	5 (1.3)

[a] Patients treated with the rivastigmine15 cm^2 patch during DB core Study DUS44 and during the open-label extension.
[b] Patients treated with the rivastigmine 5 cm^2 patch during DB core Study DUS44 and the rivastigmine15 cm^2 patch during the open-label extension.
Preferred terms are presented in descending frequency in the rivastigmine 15 cm^2/15 cm^2 column.
A patient with multiple occurrences of an adverse event was counted only once in the AE category.
Only adverse events started on or after the date of first application of study medication were included.

Common AEs over time

A decrease in the overall incidence of AEs over time (Core: 74.6% vs. Extension: 57.9%) was observed when compared common AEs reported in patients treated with the rivastigmine 15 cm2 patch during the 24 weeks of core study DUS44 and during the 24-week extension study DUS44E1. With the exception of urinary tract infection, weight decreased, syncope and muscular weakness the incidence of all common AEs decreased over time. The incidence rates for the majority of events were at least 50% lower during the extension study compared to the core study.
The greatest decreases (>3%) from core to extension were for AEs of application site erythema (13.2% vs. 1.5%), agitation (11.5% vs. 4.6%, respectively), application site dermatitis (7.6% vs. 2.0% respectively), insomnia (7.0% vs. 2.0% respectively), nausea (6.2% vs.1.5% respectively), vomiting (7.0% vs. 3.0%, respectively), diarrhoea (6.5% vs. 2.5%, respectively), anxiety (4.5% vs. 1.0 % respectively), and depression (4.8% vs. 1.0%, respectively).

Severity of AEs

During the 24-week Study DUS44E1, the majority of patients reported AEs of mild to moderate severity with 9.8% reporting severe events; except for an AE of abdominal pain in 2 patients in the 5 cm2 /15 cm2 group, dehydration, hip fracture, and cerebrovascular accident each in 2 patients in the 15 cm2 /15 cm2 group, severe AEs were single-patient events.

Table 2-9 Number (%) of patients with AEs by maximum severity, treatment group and study (24-week Study DUS44E1 –Safety population for open-label extension)

	Rivastigmine 15 cm^2/15 cm^2 [(a)] N = 197 n (%)	Rivastigmine 5 cm^2/15 cm^2 [(b)] N = 199 n (%)	Total N = 396 n (%)
Patients with mild* AEs	52 (26.4)	55 (27.6)	107 (27.0)
Patients with moderate* AEs	41 (20.8)	46 (23.1)	87 (22.0)
Patients with severe* AEs	21 (10.7)	18 (9.0)	39 (9.8)

[(a)] Patients treated with the rivastigmine15 cm^2 patch during DB core Study DUS44 and during the open-label extension.
[(b)] Patients treated with the rivastigmine 5 cm^2 patch during DB core Study DUS44 and the rivastigmine15 cm^2 patch during the open-label extension.
Any AE starting on or after the first dose in DB phase is included in this table. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple severity ratings for an AE while on a treatment is only counted under the maximum rating.

Dataset C: Study DUS44 + Study DUS44E1, 48-week safety data

During the 48 Weeks of Study DUS44 (core) plus Study DUS44E1 (extension), the overall incidence rate of AEs was slightly higher in the 15 cm2/15 cm2group (83.8%) than in the 5 cm2/15 cm2group (80.4%).

The percentages of patients with AEs in the Psychiatric disorders SOC were higher in the 15 cm2/15 cm2 group (38.1%) than in the 5 cm2/15 cm2 group (31.2%). The percentages of patients with AEs in the Infections and infestations SOC were lower in the 15 cm2/15 cm2 group than in the 5 cm2/15 cm2 group. In the General disorders and administration site conditions, Nervous system disorders, and Investigations SOCs, the incidence rates of AEs were approximately 2 to 3% higher in the 15 cm2/15 cm2 group. The percentages of patients with AEs in the Gastrointestinal disorders and Injury, poisoning and procedural complications SOCs were similar in both treatment groups.

Table 2-10 AEs by primary system organ class and treatment group (24-week Study DUS44 and 24 Week Study DUS44E1 –Safety population for open-label extension)

Primary system organ class	Rivastigmine 15 cm^2/15 cm^2 [(a)] N = 197 n (%)	Rivastigmine 5 cm^2 /15 cm^2 [(b)] N = 199 n (%)	Total N = 396 n (%)
Total number of patients with AE(s)	165 (83.8)	160 (80.4)	325 (82.1)
General disorders and administration site conditions	75 (38.1)	72 (36.2)	147 (37.1)
Psychiatric disorders	75 (38.1)	62 (31.2)	137 (34.6)
Infections and infestations	53 (26.9)	64 (32.2)	117 (29.5)
Gastrointestinal disorders	51 (25.9)	53 (26.6)	104 (26.3)
Nervous system disorders	48 (24.4)	44 (22.1)	92 (23.2)
Investigations	46 (23.4)	41 (20.6)	87 (22.0)
Injury, poisoning and procedural complications	39 (19.8)	37 (18.6)	76 (19.2)
Metabolism and nutrition disorders	28 (14.2)	24 (12.1)	52 (13.1)
Musculoskeletal and connective tissue disorders	24 (12.2)	21 (10.6)	45 (11.4)
Renal and urinary disorders	24 (12.2)	24 (12.1)	48 (12.1)
Skin and subcutaneous tissue disorders	22 (11.2)	15 (7.5)	37 (9.3)
Vascular disorders	20 (10.2)	18 (9.0)	38 (9.6)
Respiratory, thoracic and mediastinal disorders	17 (8.6)	21 (10.6)	38 (9.6)
Cardiac disorders	12 (6.1)	10 (5.0)	22 (5.6)
Eye disorders	7 (3.6)	4 (2.0)	11 (2.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (3.0)	5 (2.5)	11 (2.8)
Blood and lymphatic system disorders	3 (1.5)	6 (3.0)	9 (2.3)
Hepatobiliary disorders	3 (1.5)	1 (0.5)	4 (1.0)
Ear and labyrinth disorders	2 (1.0)	1 (0.5)	3 (0.8)
Reproductive system and breast disorders	2 (1.0)	2 (1.0)	4 (1.0)
Immune system disorders	1 (0.5)	0	1 (0.3)
Social circumstances	1 (0.5)	0	1 (0.3)
Surgical and medical procedures	1 (0.5)	2 (1.0)	3 (0.8)
Congenital, familial and genetic disorders	0	1 (0.5)	1 (0.3)
Endocrine disorders	0	2 (1.0)	2 (0.5)

[(a)] Patients treated with the rivastigmine15 cm^2 patch during DB core Study DUS44 and during the open-label extension.

[(b)] Patients treated with the rivastigmine 5 cm^2 patch during DB core Study DUS44 and the rivastigmine15 cm^2 patch during the open-label extension.

System Organ Classes are presented in descending frequency in the rivastigmine 15 cm^2/15 cm^2 column
A patient with multiple occurrences of an adverse event was counted only once in the AE category.
A patient with multiple adverse events within a system organ class was counted only once in the total row.
Only adverse events started on or after the date of first application of study medication were included.

Frequent AEs

No unexpected AEs were reported. Of the commonly observed AEs (at least 3% in either treatment group), the most frequent events (>10%) in both the 15 cm2/15 cm2 and the 5 cm2/15 cm2 group were urinary tract infection, application site erythema, agitation, weight decreased, fall and application site dermatitis. Of these most frequent events, only application site erythema, fall and weight decreased were observed in a greater percentage of patients (approximately 2%) in 15 cm2/15 cm2 compared to the 5 cm2/15 cm2 group.
The incidence rates of nausea, vomiting and diarrhoea in the 15 cm2/15 cm2 group were slightly lower compared to 5 cm2/15 cm2 group. Decreased appetite was reported more frequently in the 15 cm2/15 cm2 group compared to the 5 cm2/15 cm2 group.

Table 2-11 **Number (%) of patients with AEs (at least 3% in either treatment group) by preferred term and study treatment group (24-week Study DUS44 and 24 Week Study DUS44E1 –Safety population for open-lab extension)**

Preferred term	Rivastigmine 15 cm^2/15 cm^2 [(a)] N = 197 n (%)	Rivastigmine 5 cm^2 /15 cm^2 [(b)] N = 199 n (%)	Total N = 396 n (%)
Total number of patients with AE(s)	165 (83.8)	160 (80.4)	325 (82.1)
Urinary tract infection	29 (14.7)	34 (17.1)	63 (15.9)
Application site erythema	28 (14.2)	24 (12.1)	52 (13.1)
Agitation	26 (13.2)	32 (16.1)	58 (14.6)
Weight decreased	25 (12.7)	22 (11.1)	47 (11.9)
Fall	25 (12.7)	20 (10.1)	45 (11.4)
Application site dermatitis	20 (10.2)	23 (11.6)	43 (10.9)
Diarrhoea	17 (8.6)	19 (9.5)	36 (9.1)
Vomiting	15 (7.6)	17 (8.5)	32 (8.1)
Insomnia	15 (7.6)	15 (7.5)	30 (7.6)
Constipation	11 (5.6)	9 (4.5)	20 (5.1)
Hypertension	11 (5.6)	9 (4.5)	20 (5.1)
Decreased appetite	11 (5.6)	5 (2.5)	16 (4.0)
Anxiety	10 (5.1)	9 (4.5)	19 (4.8)
Depression	10 (5.1)	9 (4.5)	19 (4.8)
Somnolence	10 (5.1)	6 (3.0)	16 (4.0)
Application site pruritus	10 (5.1)	5 (2.5)	15 (3.8)
Urinary incontinence	9 (4.6)	12 (6.0)	21 (5.3)
Upper respiratory tract infection	9 (4.6)	7 (3.5)	16 (4.0)
Nausea	8 (4.1)	11 (5.5)	19 (4.8)
Application site irritation	8 (4.1)	4 (2.0)	12 (3.0)
Abnormal behaviour	8 (4.1)	2 (1.0)	10 (2.5)
Confusional state	7 (3.6)	9 (4.5)	16 (4.0)
Hallucination	7 (3.6)	9 (4.5)	16 (4.0)
Laceration	7 (3.6)	4 (2.0)	11 (2.8)
Oedema peripheral	6 (3.0)	10 (5.0)	16 (4.0)
Contusion	6 (3.0)	9 (4.5)	15 (3.8)
Bronchitis	6 (3.0)	6 (3.0)	12 (3.0)
Dehydration	6 (3.0)	6 (3.0)	12 (3.0)
Abdominal pain	6 (3.0)	5 (2.5)	11 (2.8)
Dizziness	5 (2.5)	8 (4.0)	13 (3.3)
Back pain	5 (2.5)	6 (3.0)	11 (2.8)
Syncope	5 (2.5)	6 (3.0)	11 (2.8)
Delusion	4 (2.0)	7 (3.5)	11 (2.8)

Headache	4 (2.0)	7 (3.5)	11 (2.8)
Hypotension	3 (1.5)	6 (3.0)	9 (2.3)
Nasopharyngitis	2 (1.0)	6 (3.0)	8 (2.0)
Mental status change	1 (0.5)	7 (3.5)	8 (2.0)
Cellulitis	1 (0.5)	6 (3.0)	7 (1.8)
Anaemia	1 (0.5)	6 (3.0)	7 (1.8)

[(a)] Patients treated with the rivastigmine15 cm^2 patch during DB core Study DUS44 and during the open-label extension.

[(b)] Patients treated with the rivastigmine 5 cm^2 patch during DB core Study DUS44 and the rivastigmine15 cm^2 patch during the open-label extension.

Preferred terms are presented in descending frequency in the rivastigmine 15 cm^2/15 cm^2 column
A patient with multiple occurrences of an adverse event was counted only once in the AE category.
Only adverse events started on or after the date of first application of study medication were included.

Other SAEs

- **Common SAEs and affected SOCs in Dataset A: Study DUS44, 24- week DB safety data.**

Psychiatric disorders
The incidence of SAEs in the Psychiatric disorder SOC was lower in the rivastigmine 15 cm2 patch group than in the rivastigmine 5 cm2 patch group (3.1% and 4.2%. respectively).
The most frequent SAE was agitation (rivastigmine 15 cm2: 2 patients (0.6%); rivastigmine 5 cm2: 5 patients (1.4%)). Aggression and depression were reported as SAEs only in the 5 cm2 group (0.8% and 0.6%, respectively).

Nervous system disorders
The incidence of nervous system related SAEs was the same in the rivastigmine 15 cm2 patch and rivastigmine 5 cm2 patch groups (3.1%).
The most frequent SAE was syncope (4 patients (1.1%) in the rivastigmine 15 cm2 group and 3 patients (0.8%) in the 5 cm2 group). Presyncope was observed in 3 (0.8%) patients in the 5 cm2 group, but not in the 15 cm2 group.

Infections & infestations
In this SOC, the incidence of SAEs was similar in the rivastigmine 15 cm2 patch and rivastigmine 5 cm2 patch groups (3.1% and 2.5%. respectively).
The most frequent SAEs were pneumonia (4 patients (1.1%) in the rivastigmine 15 cm2 group and 2 (0.6%) in the rivastigmine 5 cm2 group) and urinary tract infection (3 patients (0.8%) in the rivastigmine 15 cm2 group and 4 (1.1%) in the rivastigmine 5 cm2 group).

Gastrointestinal Disorders
In the Gastrointestinal disorders SOC the incidence of SAEs were higher in the rivastigmine 15 cm2 patch and rivastigmine 5 cm2 patch groups (2.8% vs. 0.6%, respectively).
The most frequent SAEs were vomiting and diarrhoea, each occurring in 3 (0.8%) patients in the rivastigmine 15 cm2 group only.

Injury, poisoning and procedural complications
The incidence of SAEs in this SOC was similar in both the rivastigmine 15 cm2 and 5 cm2 patch groups (2.5% vs. 3.3%, respectively).
The most frequent SAE was fall, reported in 6 patients (1.7%) in the rivastigmine 15 cm2 patch group and 5 (1.4%) patients in the rivastigmine 5 cm2 patch group.

Metabolism and nutrition disorders
The incidence of SAEs in this SOC was higher in the rivastigmine 15 cm2 patch than in the rivastigmine 5 cm2 patch groups (2.5% and 0.6%. respectively).
An SAE of dehydration was reported in 4 patients (1.1%) in the rivastigmine 15 cm2 patch group compared to 1 (0.3%) patients in the rivastigmine 5 cm2 patch group. Decreased appetite was only reported as an SAE in the rivastigmine 15 cm2 patch group; n= 2 (0.6%).

Cardiac disorders
In this SOC, the incidence of SAEs was slightly higher in the rivastigmine 15 cm2 patch group than in the rivastigmine 5 cm2 patch group (2.3% vs. 1.7%, respectively).
The only SAEs reported in more than 1 patient (≥0.5%) were bradycardia and sinus bradycardia in the rivastigmine 15 cm2 patch group (each in 2 patients [0.6%]).

- **Common SAEs in Dataset B: Study DUS44E1, 24-week open-label extension safety data.**

Nervous system disorders
The incidence of nervous system related SAEs was higher in the rivastigmine 15 cm2/15 cm2 patch group than in the rivastigmine 5 cm2/15 cm2 patch group (6.6% vs. 4.5%, respectively).
The most frequent SAE was syncope (4 patients (2.0%) in the rivastigmine 15 cm2 group and 3 patients (1.5%) in the 5 cm2 group). Cerebrovascular accident was reported for 3 (1.5%) patients in the 15 cm2/15 cm2 patch group and 1 (0.5%) patient in the 5 cm2/15 cm2 patch group and transient ischemic attack was reported for 2 (1.0%) of patients in the 15 cm2/15 cm2 group and 1 (0.5%) patient in the 5 cm2/15 cm2 patch group. Convulsion was only reported in the 5 cm2/15 cm2 group (n=2, 1.0%).

Injury, poisoning and procedural complications
The incidence of SAEs in the Injury, poisoning and procedural complications SOC was higher in the rivastigmine 15 cm2/15 cm2 patch group than in the rivastigmine 5 cm2/15 cm2 patch group (4.6% vs. 2.0%, respectively).
Fall was reported for 2 (1.0%) patients in both treatment groups. Hip fracture was reported only in the 15 cm2/15 cm2 patch group (n=2, 1.0%) and rib fracture was only reported in the 5 cm2/15 cm2 group (n=2, 1.0%).

Metabolism and nutrition disorders
The incidence of SAEs related to the Metabolism and nutrition disorders SOC was the same in both treatment groups (2.0%).
Dehydration was reported for 2 (1.0%) patients in the 15 cm2/15 cm2 patch group and 3 (1.5%) patients in the 5 cm2/15 cm2 patch group.

Cardiac disorders
SAEs in this SOC were reported in the same percentage of patients in both treatment groups (2.0%).
Cardiac failure congestive was only reported in the 5 cm2/15 cm2 patch group (n=2, 1.0%).

- **Common SAEs in Dataset C: Study DUS44+Study DUS44E1, 48-week safety data**

Nervous system disorders
The incidence of nervous system SAEs was higher in the rivastigmine 15 cm2/15 cm2 patch group than in the rivastigmine 5 cm2/15 cm2 group (7.1% and 5.0%, respectively).
In the 15 cm2/15 cm2 patch group, SAEs of syncope (n=4, 2.0%) cerebrovascular accident (n=3, 1.5%), and transient ischemic attack (n=3, 1.5%) were reported.
In the 5 cm2/15 cm2 patch group syncope, was reported in 3 (1.5%) patients, mental impairment, somnolence and convulsion were each reported 2 (1.0%) patients.
Cerebrovascular accident and transient ischemic attack were each single-patient events.

Injury, poisoning and procedural complications
In this SOC, the incidence of SAEs was higher in the rivastigmine 15 cm2/15 cm2 patch group than in the rivastigmine 5 cm2/15 cm2 group (4.6% and 3.5%, respectively).
Fall, subdural hematoma and hip fracture were each reported in 2 (1.0%) patients in the 15 cm2/15 cm2 patch group.
In the 5 cm2/15 cm2 patch group fall was reported in 3 (1.5%) patients. Subdural hematoma and rib fracture was each reported in 2 (1.0%) patients.

Infections and infestations
SAEs related to infections and infestations were lower in the rivastigmine 15 cm2/15 cm2 patch group than in the rivastigmine 5 cm2/15 cm2 group (3.0% and 6.0%, respectively).
Urinary tract infection occurred in 3 (1.5%) patients in the 15 cm2/15 cm2 patch group and 5 (2.5%) patients in the 5 cm2/15 cm2 group. Pneumonia was reported in 2 (1.0%) patients in the 15 cm2/15 cm2 group and 3 (1.5%) in the 5 cm2/15 cm2 group. Bronchitis was reported in
2 (1.0%) patients in the 5 cm2/15 cm2 patch group and was a single-patient event in the 15 cm2/15 cm2 patch group.

Cardiac disorders
The incidence rates of cardiac-related SAEs were similar in the rivastigmine 15 cm2/15 cm2 patch group and the rivastigmine 5 cm2/15 cm2 group (2.5% and 2.0%, respectively).
In the 15 cm2/15 cm2 patch group all SAEs were single-patient events.
In the 5 cm2/15 cm2 patch group atrial fibrillation and 'cardiac failure congestive' was each reported in 2 (1.0%) patients. Otherwise, all SAEs in this treatment group were single-patient events.

AEs leading to discontinuation

- **Common AEs leading to discontinuation in Dataset A: Study DUS44, 24-week DB safety data.**

The percentage of patients with AEs leading to discontinuation during the 24 weeks of Study DUS44 was higher in the rivastigmine 15 cm2 patch group compared to the rivastigmine 5 cm2 patch group (20.6% vs. 14.5%, respectively). The most frequently affected SOCs were Psychiatric disorders, Nervous system disorders, General disorders and administration site conditions and Gastrointestinal disorders**.**
The most frequent AE leading to discontinuation was agitation, which was reported in a similar percentage of patients in both the 15 cm2 and 5 cm2 patch groups (2.8% and 2.2%, respectively). This was followed by vomiting (2.5% and 1.1%, respectively), nausea (1.7% and 1.1%, respectively), decreased appetite (1.7% and 0.0%, respectively), fall, aggression, syncope and weight decreased (each 1.1% and 0.3%, respectively), and confusional state (0.8% and 1.1%, respectively).

- **Common AEs leading to discontinuation in Dataset B: Study DUS44E1 24-week open-label extension safety data.**

In study DUS44E1, the percentage of patients with AEs leading to discontinuation during the 24 weeks of was similar in the rivastigmine 15 cm2/15 cm2 patch group and 5 cm2/15 cm2 groups (11.2% vs. 12.1%, respectively).
Only 7 AEs leading to discontinuation were reported in ≥1% of patients in either treatment group: 1 cerebrovascular accident and nausea were reported in the 15 cm2/15 cm2 patch group), nausea and vomiting and diarrhoea were each reported in 4 patients, abdominal pain, somnolence and dizziness were each reported in 2 patients in the 5 cm2/15 cm2 patch group.

- **Common AEs leading to discontinuation in Dataset C: Study DUS44+Study DUS44E1, 48-week safety data**

As patients who discontinued during the core study DUS44 could not participate in the extension study DUS44E1, data on AEs leading to discontinuation that are relevant to long-term exposure to the rivastigmine 15 cm2 patch are covered by Dataset B (>24 weeks).

Deaths

There were 2 (0.3%) deaths during the 24 weeks of Study DUS44. Neither death was attributed by the investigator to study treatment. 14 patients (7 in each group) died after the last dose of study medication.

During the 24-weeks of study DUS44E1 there were 4 (1.0%) deaths. All occurred in patients in the 15 cm2/15 cm2 patch group. None of the deaths were attributed by the investigator to study treatment (chemical poisoning, cardiac arrest, cardio-respiratory arrest and dementia Alzheimer's type).
7 patients died after the last dose of study medication.

In all cases, patient's history could have explained the fatal event. Moreover, cardiac failure, cerebrovascular accident, respiratory failures are common causes of death in the general elderly population and are already reported as identified or potential risks in the RMP.

Overdose

One case of overdose in a 74 year-old female Caucasian patient was reported in Study DUS44. On Day 143, at an unscheduled visit, the investigator noted that the caregiver had applied 2 patches to the patient, both from the same box. The event was reported as a mild nonserious AE of

overdose. At the time of the event, the patient was receiving the maintenance dose of study drug (4.6 mg [5 cm2] patch with placebo [15 cm2] patch). On Day 145, the patient experienced a mild AE of skin induration that was suspected to be related to study drug. She was treated with neotracin and the event resolved the next day. An ongoing AE of moderate contact dermatitis was reported on Day 150, which was suspected to be related to study drug. The patient completed the study and received the last dose of study medication on Day 170.

Potential and identified risks

Consistent with current Risk Management Plan, the safety databases for Study DUS44 were searched for the identified risks shown in by SMQ and/or preferred terms.

- **Risks in Dataset A: Study DUS44, 24-week DB safety data.**

No events corresponding to the following risk categories were identified in ≥0.5% of patients in either treatment group: gastrointestinal ulceration, haemorrhage and perforation, medication misuse, or pancreatitis.
Risks identified during the 24 weeks of Study DUS44 were consistent with the known safety profile of the rivastigmine patch. With the exception of 'Gastrointestinal symptoms (nausea, vomiting, diarrhoea)', and 'Application site skin reactions and irritations' and 'Worsening of motor symptoms associated with Parkinson's disease', the percentages of patients with events corresponding to the remaining risks were low.
The overall incidence of dehydration events was higher in the rivastigmine 15 cm2 patch group than in the rivastigmine 5 cm2 group (3.4% vs. 2.2%, respectively) as were the overall incidence rates of cerebrovascular accident (1.4% vs. 0.3%), hypertension (4.2% vs. 3.1%), liver disorders (1.7% vs. 0.6%), pulmonary infections (3.1% vs. 1.9%), and worsening of motor symptoms associated with Parkinson's disease (9.3% vs. 7.2%).
The percentages of patients with events in the following risk categories were higher in the 5 cm2 patch group than the 15 cm2 group: cardiac arrhythmias, exacerbation of asthma and COPD, hallucinations, medication errors, myocardial infarction, seizures, severe skin reactions, and syncope and loss of consciousness.

- **Risks in Dataset B: Study DUS44E1, 24-week open-label extension safety data.**

No events corresponding to the following risk categories were identified in ≥1.0% of patients in either treatment group: exacerbations of asthma and COPD, liver disorders, medication errors, medication misuse, pancreatitis, or severe skin reactions.
Risks identified during the 24 weeks of Study DUS44E1 were consistent with the known safety profile of the rivastigmine patch. With the exception of 'Gastrointestinal symptoms (nausea, vomiting, diarrhoea)', the percentages of patients with events corresponding to the remaining risks were low.
The percentage of patients with events in the application site skin reactions and irritations risk category was similar in the 15 cm2/15 cm2 patch group and the rivastigmine 5 cm2/15 cm2 group (5.6% vs. 5.5%, respectively), as it was for worsening of motor symptoms associated with Parkinson's disease (5.1% vs. 6.0%, respectively). The percentage of patients with events in the cardiac arrhythmias risk category was higher in the 15 cm2/15 cm2 patch group than in the 5 cm2/15 cm2 group (6.1% vs. 4.0%, respectively) as it was in the cerebrovascular accident (3.6% vs. 1.0%, respectively), gastrointestinal ulceration haemorrhage, and perforation (1.0% vs. 0%, respectively), hypertension (3.6% vs. 2.0%, respectively), syncope and loss of consciousness (3.0% vs. 1.5%, respectively), and myocardial infarction (1.0% vs. 0%, respectively) risk categories.
The percentages of patients with events in the following risk categories were higher in the 5 cm2/15 cm2 patch group than the 15 cm2/15 cm2 group: acute renal failure, dehydration, gastrointestinal symptoms, hallucination, pulmonary infections, and seizures.

- **Risks in Dataset C 48: Study DUS44+Study DUS44E1, 48-week safety data**

No events corresponding to the following risk categories were identified in ≥1.0% of patients in either treatment group: medication errors, medication misuse, pancreatitis, or severe skin reactions.
Risks identified during the combined 48 weeks of Study DUS44 and Study DUS44E1 were consistent with the known safety profile of the rivastigmine patch. With the exception of 'Application site skin reactions and irritations', and 'Gastrointestinal symptoms (nausea, vomiting,

diarrhea)' and 'Worsening of motor symptoms associated with Parkinson's disease', the percentages of patients with events corresponding to the remaining risks were low.
The percentage of patients with events in the acute renal failure risk category was similar in the 15 cm2/15 cm2 patch group and the rivastigmine 5 cm2/15 cm2 group (1.5% vs. 1.0%, respectively), as it was for cardiac arrhythmias (7.6% vs. 7.0%, respectively), pulmonary infections (5.1% vs. 5.5%, respectively), and syncope and loss of consciousness (3.6% vs. 3.0%, respectively).
The percentage of patients with events in the application site skin reactions and irritations risk category was higher in the rivastigmine 15 cm2/15 cm2 group than in the 5 cm2/15 cm2 group (31.0% vs. 27.6%, respectively), as it was in the cerebrovascular accident (5.1% vs. 1.0%, respectively), gastrointestinal ulceration, haemorrhage and perforation (1.0% vs. 0%, respectively), hypertension (7.1% vs. 6.0%, respectively), liver disorders (2.5% vs. 1.0%, respectively), myocardial infarction (1.0% vs. 0%, respectively), and worsening of motor symptoms associated with Parkinson's disease (15.2% vs. 11.1%, respectively), risk categories.
The percentages of patients with events in the following risk categories were higher in the 5 cm2/15 cm2 patch group than the 15 cm2/15 cm2 group: dehydration, exacerbations of asthma and COPD, gastrointestinal symptoms, pulmonary infections, hallucinations, and seizures.

Laboratory findings

Haematology, chemistry, urinalysis

During the Study DUS44 and DUS44E1, there were no clear trends of clinically meaningful changes in haematology variables in either treatment group.

During the Study DUS44 and DUS44E1 there were no clear trends of clinically meaningful changes in clinical chemistry variables in either treatment group.
During the Study DUS44 and DUS44E1 there were no clear trends of clinically meaningful changes in urinalysis.

Vital signs, body weight and physical examinations

A clinically notable decrease in weight (≥ 7%) was observed in a higher percentage of patients in the rivastigmine 15 cm2/15 cm2 patch group, than in the rivastigmine 5 cm2/15 cm2 group (25.9 %. vs. 23.2%, respectively) in study DUS44E1. A clinically notable increase in weight (≥ 7%) was observed in a similar percentage of patients in the rivastigmine 15 cm2/15 cm2 patch group, than in the rivastigmine 5 cm2/15 cm2 group (11.4 %. vs. 12.9%, respectively).

Electrocardiograms

Clinically notable between-group differences in ECG values were observed for QTcF intervals, QRS duration, and PQ/PR ratios in study DUS44. None of the notable values was reported as an AE.
In study DUS44E1 clinically notable decreases or increases in QT were observed in similar percentages in both groups as well as clinically notable decreases in QRS.
QT prolongation and unlisted cardiac arrhythmias are issues that are under closed monitoring and will be discussed in the next PSUR.

Safety in specials groups

o **Dataset D Study D2340 (post-hoc subgroup analysis in severe patients): 48-week DB safety data**

Common AEs: 48 Week-DB safety data.

During the 48-Week DB phase of Study D2340, the most frequently affected SOCs for severe patients were Psychiatric disorders, Nervous system disorders, Gastrointestinal disorders, General disorders and administration site conditions and Infections and infestations.

The percentage of severe patients with Psychiatric disorders or Nervous system disorders events was higher in the rivastigmine 15 cm2 patch group compared to the rivastigmine 10 cm2 patch group (33.0% vs. 23.9%, respectively and 26.2% and 19.6%, respectively). The percentage of severe patients with AEs in the Gastrointestinal disorders, General disorders and administration site conditions, or Infections and infestations SOC was higher in the 10 cm2 patch group compared to the 15 cm2 group.

Table 5-1 **AEs (at least 1% in either group) by primary system organ class and treatment group in severe patients (MMSE <=12 at DB-baseline) (Study D2340, 48 weeks-DB Safety population)**

Primary system organ class	Rivastigmine 15 cm^2 patch N=103 n (%)	Rivastigmine 10 cm^2 patch N=92 n (%)	Total N=195 n (%)
Any primary system organ class	79 (76.7)	61 (66.3)	140 (71.8)
Psychiatric disorders	34 (33.0)	22 (23.9)	56 (28.7)
Nervous system disorders	27 (26.2)	18 (19.6)	45 (23.1)
Gastrointestinal disorders	20 (19.4)	21 (22.8)	41 (21.0)
General disorders and administration site conditions	17 (16.5)	20 (21.7)	37 (19.0)
Infections and infestations	17 (16.5)	17 (18.5)	34 (17.4)
Injury, poisoning and procedural complications	15 (14.6)	12 (13.0)	27 (13.8)
Metabolism and nutrition disorders	14 (13.6)	11 (12.0)	25 (12.8)
Investigations	9 (8.7)	3 (3.3)	12 (6.2)
Renal and urinary disorders	8 (7.8)	4 (4.3)	12 (6.2)
Respiratory, thoracic and mediastinal disorders	7 (6.8)	3 (3.3)	10 (5.1)
Musculoskeletal and connective tissue disorders	6 (5.8)	12 (13.0)	18 (9.2)
Vascular disorders	5 (4.9)	5 (5.4)	10 (5.1)
Cardiac disorders	3 (2.9)	7 (7.6)	10 (5.1)
Ear and labyrinth disorders	2 (1.9)	1 (1.1)	3 (1.5)
Skin and subcutaneous tissue disorders	2 (1.9)	6 (6.5)	8 (4.1)
Blood and lymphatic system disorders	1 (1.0)	1 (1.1)	2 (1.0)
Endocrine disorders	1 (1.0)	1 (1.1)	2 (1.0)
Eye disorders	1 (1.0)	3 (3.3)	4 (2.1)
Hepatobiliary disorders	1(1.0)	0	1(0.5)
Immune system disorders	0	3(3.3)	3(1.5)
Neoplasms, benign, malignant and unspecified (incl cysts and polyps)	0	2(2.2)	2 (1.0)
Reproductive system and breast disorders	0	1(1.1)	1 (0.5)
Social circumstances	0	1(1.1)	1 (0.5)

System Organ Classes are presented in descending frequency in the 15 cm^2 column
A patient with multiple occurrences of an adverse event was counted only once in the AE category.
A patient with multiple adverse events within a system organ class was counted only once in the total row.
Only adverse events started on or after the date of first application of study medication were included.

Frequent AEs

During the 48-Week DB phase of Study D2340 no unexpected AEs were reported in the severe subpopulation. Of the commonly observed AEs (at least 3% in either treatment group) the most frequent events (>5%) for severe patients in the rivastigmine 15 cm2 patch group were fall, anxiety, insomnia, depression, dizziness, urinary tract infection, decreased appetite, nausea , vomiting.

Except for vomiting these events were observed more frequently in the 15 cm2 patch group compared to the 10 cm2 group.

Table 5-2 Number (%) of patients with AEs (at least 3% in either treatment group), by preferred term and treatment group in severe patients (MMSE <=12 at DB-baseline) (Study D2340, 48 weeks-DB Safety population)

Preferred term	Rivastigmine 15 cm^2 patch N=103 n (%)	Rivastigmine 10 cm^2 patch N=92 n (%)	Total N=195 n (%)
Total number of patients with AE(s)	79 (76.7)	61 (66.3)	140 (71.8)
Fall	11 (10.7)	8 (8.7)	19 (9.7)
Anxiety	8 (7.8)	3 (3.3)	11 (5.6)
Insomnia	8 (7.8)	3 (3.3)	11 (5.6)
Depression	7 (6.8)	1 (1.1)	8 (4.1)
Dizziness	7 (6.8)	0	7 (3.6)
Urinary tract infection	7 (6.8)	4 (4.3)	11 (5.6)
Decreased appetite	6 (5.8)	3 (3.3)	9 (4.6)
Nausea	6 (5.8)	5 (5.4)	11 (5.6)
Vomiting	6 (5.8)	6 (6.5)	12 (6.2)
Agitation	5 (4.9)	7 (7.6)	12 (6.2)
Application site erythema	5 (4.9)	4 (4.3)	9 (4.6)
Constipation	5 (4.9)	3 (3.3)	8 (4.1)
Nasopharyngitis	5 (4.9)	2 (2.2)	7 (3.6)
Oedema peripheral	5 (4.9)	3 (3.3)	8 (4.1)
Psychomotor hyperactivity	5 (4.9)	8 (8.7)	13 (6.7)
Urinary incontinence	5 (4.9)	1 (1.1)	6 (3.1)
Weight decreased	5 (4.9)	2 (2.2)	7 (3.6)
Aggression	4 (3.9)	5 (5.4)	9 (4.6)
Dehydration	4 (3.9)	3 (3.3)	7 (3.6)
Diarrhoea	4 (3.9)	4 (4.3)	8 (4.1)
Hypotension	4(3.9)	1(1.1)	5(2.6)
Tremor	4(3.9)	1(1.1)	5(2.6)
Gastrooesophageal reflux disease	2(1.9)	3(3.3)	5(2.6)
Hypertension	2(1.9)	3(3.3)	5(2.6)
Confusional state	1(1.0)	4(4.3)	5(2.6)
Application site pruritus	0	4 (4.3)	4 (2.1)
Hypoglycaemia	0	3 (3.3)	3 (1.5)
Musculoskeletal chest pain	0	3 (3.3)	3 (1.5)

Preferred terms are sorted by descending frequency in the rivastigmine 15 cm^2 treatment group.
A patient with multiple occurrences of AE was counted only once in the AE category.
Only AEs occurring at or after first drug intake were included.

Common AEs over time

A comparison of common AEs reported in severe patients treated with the rivastigmine 15 cm2 patch during the first 24 weeks and during the period after Week 24 of Study D2340 showed that the overall incidence of AEs decreased over time (first 24 weeks: 65.0% vs. >24 weeks: 46.0%). The incidence rates for the majority of events were lower during the period after Week 24 compared to the first 24 weeks. The most notable decreases were for AEs of dizziness, vomiting, agitation, application site erythema, tremor, hallucination and headache.

Table 5-3 **Common AEs over time in severe patients (MMSE <=12 at DB-baseline) treated with the rivastigmine 15 cm^2 patch (at least 2% in either treatment group) by preferred term (Study D2340, -DB Safety population)**

Preferred term	Rivastigmine 15 cm^2 patch (DB W 0-24) N=103 n (%)	Rivastigmine 15 cm^2 patch (DB W >24) N=87 n (%)
Total number of patients with AE(s)	67 (65.0)	40 (46.0)
Dizziness	6 (5.8)	1 (1.1)
Fall	6 (5.8)	5 (5.7)
Vomiting	6 (5.8)	0
Anxiety	5 (4.9)	3 (3.4)
Decreased appetite	5 (4.9)	1 (1.1)
Urinary tract infection	5 (4.9)	3 (3.4)
Agitation	4 (3.9)	1 (1.1)
Application site erythema	4 (3.9)	1 (1.1)
Depression	4 (3.9)	3 (3.4)
Nausea	4 (3.9)	2 (2.3)
Psychomotor hyperactivity	4 (3.9)	3 (3.4)
Tremor	4 (3.9)	1 (1.1)
Dehydration	3 (2.9)	1 (1.1)
Diarrhoea	3 (2.9)	1 (1.1)
Hallucination	3 (2.9)	0
Headache	3 (2.9)	0
Aggression	2 (1.9)	2 (2.3)
Constipation	2 (1.9)	3 (3.4)
Hypertension	2 (1.9)	0
Insomnia	2 (1.9)	6 (6.9)
Nasopharyngitis	2 (1.9)	3 (3.4)
Oedema peripheral	2 (1.9)	3 (3.4)
Urinary incontinence	2 (1.9)	3 (3.4)
Weight decreased	2 (1.9)	3 (3.4)
Hypotension	2 (1.9)	2 (2.3)
Hallucination, visual	1 (1.0)	2 (2.3)
Irritability	0	2 (2.3)

Preferred terms are sorted by descending frequency in the rivastigmine 15 cm^2 treatment group.
A patient with multiple occurrences of AE was counted only once in the AE category.
Only AEs occurring at or after first drug intake were included.

Severity of AEs

During 48 weeks of Study D2340, the majority of severe patients reported AEs of mild to moderate severity with severe events reported for 16.5% of patients in the 15 cm2 patch group and 14.1% in the 10 cm2 patch group. With the exception of severe AEs of agitation (15 cm2: 1.9%; 10 cm2: 2.2%), hyperglycaemia (15 cm2: 0%; 10 cm2: 2.2%), vomiting (15 cm2: 1.0%; 10 cm2: 2.2%), and dehydration (15 cm2: 2.0%; 10 cm2: 0%), all AEs reported as severe were single-patient events in both treatment groups.

Deaths

In severe patients, during the 48-week DB phase of Study D2340, there were 2 (1.9%) deaths in the rivastigmine 15 cm2 patch group and 2 (2.2%) deaths in the rivastigmine 10 cm2 group. None of the deaths were attributed by the investigator to study treatment.

Common SAEs: 48-week DB safety data

The overall incidence of SAEs was substantially lower in the rivastigmine 15 cm2 patch group compared to the 10 cm2 group (15.5% and 22.8%, respectively).
No unexpected SAEs were reported. No pattern of events was observed that would suggest a relationship between the rivastigmine patch dose and SAEs reported.

The incidence rates of SAEs in the most frequently affected SOCs for the 15 cm2 patch and 10 cm2 patch groups were: Nervous system disorders; Injury, poisoning and procedural complications; Psychiatric disorders, and Infections and infestations.

The most frequently reported SAEs in the rivastigmone 15 cm2 patch group were aggression, fall and hypotension, each reported in 1.9% of patients. In the 5 cm2 patch SAEs of aggression and fall were reported in 2.2% and 1.1% of patients, respectively. Hypotension was not reported in this group.

Table 5-5 Number (%) of severe patients with SAEs (at least 1.5% in either treatment group), by preferred term and treatment group (Study D2340 48-week DB phase -Safety population)

Preferred term	Rivastigmine 15 cm^2 patch N = 103 n (%)	Rivastigmine 10 cm^2 patch N = 92 n (%)	Total N = 195 n (%)
Total number of patients with AE(s)	16 (15.5)	21 (22.8)	37 (19.0)
Aggression	2 (1.9)	2 (2.2)	4 (2.1)
Fall	2 (1.9)	1 (1.1)	3 (1.5)
Hypotension	2 (1.9)	0	2 (1.0)
Agitation	1 (1.0)	2 (2.2)	3 (1.5)
Dementia Alzheimer's type	0 (0.0)	2 (2.2)	2 (1.0)
Hip fracture	0	2 (2.2)	2 (1.0)
Suicidal ideation	0	2 (2.2)	2 (1.0)
Hyperglycaemia	0	2 (2.2)	2 (1.0)
Sick sinus syndrome	0	2 (2.2)	2 (1.0)

SAEs occurring in more than 1.5% in either treatment group are presented in descending frequency of rivastigmine 15 cm^2.

A patient with multiple occurrences of an SAE under one treatment is counted only once in the SAE category for that treatment.

AEs leading to discontinuation: 48-week DB safety data.

Overall, the percentage of severe patients with AEs leading to discontinuation during the full 48 weeks of Study D2340 was 7.8% in the rivastigmine 15 cm2 patch group and 16.9% the 10 cm2 patch group. The most frequently affected SOCs were Nervous system disorders (15 cm2 patch group: 3.9%; 10 cm2 patch group: 4.3%), and Psychiatric disorders (15 cm2 patch group: 1.9%; rivastigmine 10 cm2 patch group: 3.3%). An AE of aggression led to discontinuation in 2 (2.2%) in the 10 cm2 patch group. Otherwise, all AEs leading to discontinuation in both treatment groups were single-patient events.

Time to discontinuation

For severe patients from Study D2340, results of the analysis of time to first AE leading to discontinuation and time to discontinuation for any reason show a small difference for both analyses in favour of the 15cm2 treatment group. Percentages of discontinuations due to AEs and due to any reason were lower for the 15 cm2 compared to the 10 cm2.

Discussion on clinical safety

The overall incidence rate of AEs in study DUS44 was similar in both treatment groups (15 cm2: 74.6%; 5 cm2: 73.3%). However, as both treatment groups received rivagstigmine it is not possible to estimate the differences to a placebo treatment.

For common AEs, the reported higher frequency in the rivastigmine 15 cm2 patch group compared to the 5 cm2 group of decreased appetite, nausea, vomiting, diarrhea, weight decreased and dehydration, with an increased risk of severe AEs noted in the 15cm2 group, could pose a physiological risk for the patients; dizziness, fall and laceration could pose a risk of trauma; and insomnia, fatigue, asthenia and somnolence could affect the cognitive function of the patients.

Several patients died within 30 days of study drug discontinuation, many as a consequence of a SAE.

The SAEs pattern could indicate a higher risk of serious dehydration, diarrhoea and vomiting when treated with the 15 cm2 patch compared to the 5 cm2 patch.

Vomiting, nausea, decreased appetite, fall and weight decreased were more common reason for discontinuation in the 15 cm2 patch group compared to in the 5 cm2 patch group.
When comparing common AEs reported in patients treated with the rivastigmine 15 cm2 patch during the 24 weeks of core study DUS44 and during the 24-week extension study DUS44E1 a decrease in the overall incidence of AEs over time is observed (Core: 74.6% vs. Extension: 57.9%). However, the incidence of urinary tract infection, weight decreased, syncope and muscular weakness did not decreased over time.

The AE pattern in this subgroup of patients with severe AD in study D2340 confirm a dose-response relationship for Psychiatric disorders, dizziness, decreased appetite and weight decrease noted in the pivotal study DUS44.

Conclusions on clinical safety

Safety data from Study DUS44 and Study DUS44E1 identify no unexpected adverse events during the 48-week treatment with Exelon patch in severe Alzheimer's disease population.
Risks identified during the 24 weeks of the double-blind phase and the 24 weeks of the extension study as well as the combined 48 weeks were consistent with the known safety profile of the rivastigmine patch.

The AE pattern of rivastigmine in patients with severe AD is similar to the AE pattern in patients with mild to moderate AD. However, when analysing the frequency of AEs and in the analysis include the frequency of SAEs and discontinuation, **application site reactions, fall, cardiac disorders, gastrointestinal disorders, metabolism and nutrition disorders, nervous system disorders and psychiatric disorders** are more common and more often more severe in the severe AD patients in study DUS44 compared to the patients with mild to moderate AD in Study 2340. This increased burden of AEs of rivastigmine in the severe AD patients compared to the patients with mild to moderate AD is of concern and of importance for the B/R evaluation.

Pharmacovigilance system

The system of pharmacovigilance that will be put in place for the line extension will be the DDPS approved on July 2011.
The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.3.1. PRAC advice

The CHMP received the following PRAC conclusions on the submitted Risk Management Plan.

Based on the PRAC review of the Risk Management Plan version 7.1 the PRAC considers by consensus that the risk management system for rivastigmine (EXELON/PROMETAX) in the treatment of

- Patients with mild to moderately severe Alzheimer's disease

and in the proposed indication

- Symptomatic treatment of severe Alzheimer's dementia

is acceptable. The following points should be taken into account in the next update:

- Study ENA713D2409 'Exelon Transdermal Patch: A Drug Utilization Study' is a category 3 study (required), Part III.4.1 and Part III.4.3 need to be revised accordingly.

This is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Gastrointestinal symptoms (nausea, vomiting, diarrhea) • Worsening of motor symptoms associated with Parkinson's disease • Pancreatitis • Cardiac arrhythmias • Exacerbations of asthma and COPD • Application site skin reactions and irritations *(only patches)* • Hypertension • Gastrointestinal ulceration, hemorrhage, and perforation • Seizures • Hallucinations • Syncope and loss of consciousness • Medication misuse *(only patches)* • Medication errors *(only patches)* • Dehydration • Liver disorders • Severe skin reactions (bullous reactions)
Important potential risks	• Cerebrovascular accident • Pulmonary infections • Myocardial infarction • Death • Acute renal failure
Missing information	None

Pharmacovigilance plans

Table 2.2: On-going and planned studies in the pharmacovigilance development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
ENA713D2409 Exelon Transdermal Patch: A Drug Utilization Study. **Category 3**	• Assessment of appropriate use and estimation of inappropriate drug use of rivastigmine patches (5 cm^2, 10 cm^2, 15 cm^2) as recorded by patients and/or their caregivers. • Assessment of titration patterns of rivastigmine patches, particularly regarding increases from a lower to a higher dose.	• Medication misuse *(only patches)* • Medication errors *(only patches)*	Planned	Final protocol July 2013;

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that study ENA713D2409 'Exelon Transdermal Patch: A Drug Utilization Study' is a category 3 study (required), Part III.4.1 and Part III.4.3 need to be revised accordingly.

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

2.4. Risk minimisation measures for EXELON/PROMETAX

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Identified risks		
Gastrointestinal symptoms (nausea, vomiting, diarrhea)	SPC Section 4.2 Posology and method of administration; Nausea, Vomiting and Diarrhea and dehydration resulting from prolonged vomiting or diarrhea are identified in the SPC Section 4.4 Special warnings and precautions for use, and Section 4.8 as Undesirable effects).	None
Worsening of motor symptoms associated with Parkinson's	Routine risk minimization (Motor symptoms are identified in the SPC	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
disease	Section 4.2 Posology and method of administration, Section 4.4 Special warnings and precautions for use and Section 4. 8 Undesirable effects).	
Pancreatitis	Routine risk minimization (Listed in SPC Section 4.8	None
Cardiac arrhythmias	Routine risk minimization (Identified in the SPC Section 4.4 as Special warnings and precautions for use and Section 4.8 as Undesirable effect).	None
Exacerbations of asthma and COPD	Routine risk minimization (Identified in the SPC Section 4.4 as Special warnings and precautions for use).	None
Application site skin reactions and irritations *(only patches)*	Instructions on how to minimize this event are provided in SPC Section 4 Posology and method of administration; Identified as an Undesirable effect in the SPC Section 4.8	None
Hypertension	Routine risk minimization (listed in SPC Section 4.8 Undesirable effects).	None
Gastrointestinal ulceration, hemorrhage, and perforation	Routine risk minimization (Identified as Special warnings and precautions for use in Section 4.4 and as Undesirable effects in Section 4.8 of the SPC).	None
Seizures	Routine risk minimization (Identified as Special warnings and precautions for use in the SPC Section 4.4 and listed in SPC Section 4.8 Undesirable effects.	None
Hallucinations	Routine risk minimization (listed in SPC Section 4.8	None
Syncope and loss of consciousness	Routine risk minimization (listed in SPC Section 4.8 Undesirable effects and section 4.9 Overdose).	None
Medication misuse *(only patches)*	Routine risk minimization (Instructions on how to use rivastigmine patch provided in SPC Section 4.2 Posology and method of administration: The transdermal patch should be replaced by a new	• Direct Healthcare Professional Communication Letter • Patient/caregiver reminder card

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	one after 24 hours. Only one transdermal patch should be worn at a time (see Section 4.9). The transdermal patch should not be cut into pieces. Patients and caregivers should be instructed accordingly. SPC section 4.9 Overdose: Symptoms Overdose with Exelon transdermal patch resulting from misuse/dosing errors (application of multiple patches at a time) has been reported in the post-marketing setting. The typical symptoms reported among these cases are similar to those seen with cases of overdose associated with Exelon oral formulations.	
Medication errors *(only patches)*	Routine risk minimization (Instructions on how to use rivastigmine patch provided in SPC Section 4.2 Posology and method of administration: The transdermal patch should be replaced by a new one after 24 hours. Only one transdermal patch should be worn at a time (see Section 4.9). The transdermal patch should not be cut into pieces. Patients and caregivers should be instructed accordingly. SPC section 4.9 Overdose: Symptoms Overdose with Exelon transdermal patch resulting from misuse/dosing errors (application of multiple patches at a time) has been reported in the post-marketing setting. The typical symptoms reported among these cases are similar to those seen with cases of overdose associated with Exelon oral formulations.	• Direct Healthcare Professional Communication Letter • Patient/caregiver reminder card
Dehydration	Routine risk minimization (Dehydration is identified in the SPC Section 4.2 Posology and method of administration, Section 4.4 Special warnings and precautions for use, and Section 4.8 as Undesirable effects).	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Liver disorders	Routine risk minimization (Identified as Special warnings and precautions for use in patients with hepatic impairment in the SPC Section 4.4 Hepatitis is listed in SPC Section 4.8 Undesirable effects from post-marketing spontaneous reports Reference made to abnormal hepatic function tests with rivastigmine oral formulations in SPC Section 4.8 for rivastigmine patches).	None
Severe skin reactions (bullous reactions)	Routine risk minimization (the following ADRs are listed in SPC Section 4.8: pruritus, rash, erythema, urticaria, blister, and dermatitis allergic).	None
Potential risks		
Cerebrovascular accident	None	None
Pulmonary infections	None	None
Myocardial infarction	None	None
Death	None	None
Acute renal failure	Routine risk minimization in SPC Section 4.2 Posology and method of administration: Renal impairment: No dose adjustment is necessary for patients with renal impairment.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

3. BENEFIT RISK ASSESSMENT

Beneficial effects

In the pivotal study ENA713DUS44 decline in cognition, as measured by the mean change from DB-baseline in SIB score, the between-treatment group differences were statistically significant in favour of the rivastigmine patch 15 cm2 group compared to the 5 cm2 patch group (4.9 points; $p<0.0001$).

For decline in function, as measured by the mean change from DB-baseline in ADCS-ADL-SIV score, the between group differences were statistically significant in favour of the rivastigmine patch 15 cm2 group at Week 24 (1.2 points; $p=0.0247$).

In study 2340 the 15 cm2 treatment group of severe AD patients showed statistical and numerical, respectively, less decline compared to the 10 cm2 group as measured by both the ADCS-Instrumental ADL subscale and the ADAS-cog.

Uncertainty in the knowledge about the beneficial effects

The clinical relevance of the measured effect on cognition is questionable.

Only one of the primary endpoints showed a statistical significant difference between the two doses groups in the patients with a baseline MMSE score of ≤ 9 points.

For the responder analysis of the primary variable SIB the between treatment group differences was statistically significant but not for the ADCS-ADL-SIV, the other primary end-point. Responder analyses for the ≤9 and >9 MMSE subgroups has not been performed.

Risks

Unfavourable effects

The AE pattern of rivastigmine in patients with severe AD is similar to the AE pattern in patients with mild to moderate AD. However, when analysing the frequency of AEs and in the analysis include the frequency of SAEs and discontinuation, **application site reactions, fall, cardiac disorders, gastrointestinal disorders, metabolism and nutrition disorders, nervous system disorders and psychiatric disorders** are more common and more often more severe in the severe AD patients in study DUS44 compared to the patients with mild to moderate AD in Study 2340. This increased burden of AEs of rivastigmine in the severe AD patients compared to the patients with mild to moderate AD is of concern and of importance for the B/R evaluation.

Uncertainty in the knowledge about the unfavourable effects

The safety pattern for the group of patients with MMSE score ≤9, potentially a better definition of patients with severe AD, has not been analysed in detail.
Balance

Importance of favourable and unfavourable effects

It is unclear how the measured effects of rivastigmine on cognitive endpoint transfer into a clinical meaningful effect. The other most important endpoint, i.e. activities of daily living fail to show statistical significant effect in the most important group of patients with severe AD (MMSE score ≤9).

Furthermore, in the intended population of severe AD patients the consequence of several of the AEs noted could be serious for the individual patient, and many of these has been shown to be dose-dependent which have bearing on the chosen dose.

Benefit-risk balance

Discussion on the benefit-risk assessment

Based on the questionable effect shown (only consistently significant difference in one primary endpoint, maybe the least important end-point for these severe AD patients in the AD population and also in patients with MMSE ≤9, and the seemingly higher frequency of AEs (including SAEs) in this vulnerable population compared to the mild to moderate AD population, the CHMP is of the opinion that the applied indication is not approvable.

3.1. Conclusions

The overall Benefit-Risk of Exelon/Prometax for symptomatic treatment of severe Alzheimer's dementia is considered to be negative.

4. PROPOSED LIST OF OUTSTANDING ISSUES TO BE ADDRESSED IN AN ORAL EXPLANATION AND/OR IN WRITING

4.1. Clinical aspects

Major objection

- The benefit/risk of Exelon transdermal patch in the treatment of severe Alzheimer's dementia is negative. The results do not support a clinical meaningful effect of rivastigmine in AD patients with MMSE >3 and<12, especially in the patient sub-group with MMSE≤9, the severe AD patient group for whom rivastigmine is not approved. Moreover, the frequency of many AEs and especially some SAEs is higher in this severe Alzheimer's dementia population. The consequences of several of the AEs noted (e.g. fall, syncope, **gastrointestinal disorders**, metabolism and nutrition disorders and psychiatric disorders) are serious and of great concern for this vulnerable population.

Other concerns

The applicant should performed the analyses of responders for the ≤9 and >9 MMSE subgroups.
Regarding the clinical relevance the MAH claim that the numerical differences for ADAS cog and ADCS-ADL are similar to what had been observed in the overall population in Study 2340, however the results in the overall population are not presented. These data should be submitted.