

Rivastigmine in the Treatment of Alzheimer's Disease and Parkinson's Disease Dementia

a report by
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Recent epidemiological evidence suggests a worldwide prevalence of 24.3 million cases of dementia, with one new case developing every seven seconds.¹ Alzheimer's disease (AD) remains the most common cause of dementia, responsible for 60–70% of cases in Europe.² In addition, around 30% of patients with Parkinson's disease (PD) are affected by dementia.³ In a 12-year population study of patients with PD, the cumulative incidence of dementia increased steadily with age and disease duration, reaching 80% by the age of 90 years (conditional on survival).⁴

Although it was previously thought that the dementia seen in PD originates from the same pathology that causes AD, recent evidence suggests that the pathologies underlying AD and dementia associated with PD (PDD) are different.⁵ While the presence of amyloid plaques and neurofibrillary tangles is characteristic of the pathology of AD, PDD has been found to be predominantly associated with Lewy body-type pathology.³ Moreover, the pathological course of the disease is different in the two dementia types, with AD typically starting in the entorhinal and transentorhinal regions and PDD starting in the brainstem.^{5,6} The different brain areas affected are also reflected in the distinct clinical profiles of PDD and AD: AD is primarily characterised by memory deficits,⁶ whereas PDD typically manifests as a dysexecutive syndrome with a predominant impairment of executive functions and attention.³

Despite these differences, cholinergic deficits are a common feature in both AD and PDD.⁷ The original hypothesis, developed to explain the symptoms seen in AD,⁸ suggests that the cognitive impairments seen in dementia are biochemically associated with cholinergic deficits. However, it has since been described that cholinergic deficits in patients with PDD may be even greater than those seen in AD patients.⁷ This provided the rationale for evaluating cholinesterase inhibitors in both conditions in clinical trials.

Rivastigmine (Exelon®, Novartis) is a cholinesterase inhibitor that is widely available as a transdermal patch, oral solution and capsules. Currently, oral rivastigmine is approved by many regulatory authorities worldwide

for the treatment of mild to moderate AD and PDD. In addition, in the past year the rivastigmine patch has been approved for the treatment of mild to moderate AD and mild to moderate PDD in a number of countries. These approvals were based on clinical trials in target populations, the results of which are reviewed here.

Pharmacology of Rivastigmine

Like other cholinesterase inhibitors, rivastigmine exerts its main action through the inhibition of cholinesterase enzymes. Reduction in the activity of these enzymes prevents the degradation of the neurotransmitter acetylcholine (ACh) after its release from the pre-synaptic neuron, thereby

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amplifying its post-synaptic action.⁹ Unlike donepezil and galantamine – which are selective inhibitors of acetylcholinesterase (AChE) – rivastigmine provides sustained inhibition of both AChE and butyrylcholinesterase (BuChE).¹⁰ BuChE activity is high in brain areas involved in various cognitive functions such as attention and executive functions.^{11,12} The dual enzyme inhibition afforded by rivastigmine may therefore be of relevance for the treatment of such deficits.¹¹ Further information about the pharmacokinetics of rivastigmine can be found in the article by Frölich, also appearing in this issue.¹³

Rivastigmine in Alzheimer's Disease

The pivotal clinical trials of oral rivastigmine were carried out in the 1990s,^{14,15} while the rivastigmine transdermal patch was developed and evaluated almost a decade later.¹⁶ It has been suggested that factors such as evolving study population profiles and refinements in clinical trial design and practice during that decade may have differentially influenced the outcomes of these studies.¹⁷

Rivastigmine Capsules

This article will focus primarily on data obtained from the two largest studies employing twice-daily doses and high dose ranges, which have been the basis of registration for rivastigmine capsules. Of these two



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Table 1: Mean Changes from Baseline at Six Months in Landmark Trials of Oral Rivastigmine and Rivastigmine Patch

Study	Dose	Patients (ITT Population)	Cognition		Activities of Daily Living	
			ADAS-cog	MMSE	ADCS-ADL	PDS
B352 ^{14,19}	Placebo	235	4.15 ^a	-0.79 ^a	–	-5.17 ^b
	Oral rivastigmine (6–12mg/day)	231	-0.79* ^a	0.30* ^a	–	-1.01* ^b
B303 ¹⁵	Placebo	239	1.41 ^a	-0.54 ^b	–	-2.23 ^b
	Oral rivastigmine (6–12mg/day)	243	-1.17** ^a	0.34* ^b	–	0.5* ^b
IDEAL ¹⁶	Placebo	302	1.0 ^c	0 ^c	-2.3 ^c	–
	Rivastigmine patch (9.5mg/24-hour)	293	-0.6* ^c	1.1 ^c	-0.1* ^c	–
	Oral rivastigmine (12mg/day)	297	-0.6* ^c	0.8 ^c	-0.5* ^c	–

ITT = intent-to-treat population; ADAS-cog = Alzheimer's Disease Assessment Scale – cognitive subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living; MMSE = Mini-Mental State Examination; PDS = Progressive Deterioration Scale; IDEAL = Investigation of transDermal Exelon in Alzheimer's disease; OC = observed cases.

* = $p < 0.05$ versus placebo; ** = $p < 0.001$ versus placebo; a = OC analysis; b = last observation carried forward (LOCF) analysis; c = ITT-LOCF analysis.

Negative mean changes on the ADAS-cog indicate improvement. Negative mean changes on the ADCS-ADL, MMSE and PDS indicate deterioration.

Table 2: Percentages of Patients Experiencing the Most Frequently Reported Adverse Events in Pivotal Clinical Trials of Rivastigmine

Adverse Event	B352 Study ^{14a}		B303 Study ¹⁵		IDEAL Study ¹⁶		
	Rivastigmine 6–12mg/day Oral	Placebo	Rivastigmine 6–12mg/day Oral	Placebo	Rivastigmine 12mg/day Oral	Rivastigmine 9.5mg/24-hour Patch	Placebo
Nausea	48*	11	50*	10	23*	7	5
Vomiting	27*	3	34*	6	17*	6	3
Dizziness	24*	13	20*	7	8*	2	2
Anorexia	20*	3	14*	2			
Headache			19*	8	6*	3	2
Diarrhoea			17*	9	5	6	3
Abdominal pain			12*	3			
Fatigue	10*	4	10*	3			
Asthenia	10*	2			6*	2	1
Malaise			10*	2			
Somnolence	9*	2					
Sweating	6*	2					
Flatulence	5*	1					
Weight loss					5*	3	1

* = $p < 0.05$ versus placebo; a = figures relate to the titration phase of treatment; IDEAL = Investigation of transDermal Exelon in Alzheimer's disease.

Only adverse events occurring in at least 5% of patients of any treatment group are recorded.

prospective, randomised, double-blind, placebo-controlled trials, one was carried out in the US (study B352)¹⁴ and the other was based mainly in Europe (study B303).¹⁵

All aspects of dementia, including activities of daily living (ADL), global status and cognition, were investigated in pivotal trials of rivastigmine oral.^{14,15} In accordance with the requirements of the US Food and Drug Administration (FDA) for AD clinical trials in the 1990s, efficacy outcomes included both a measure of the improvement on a performance-based cognitive instrument, i.e. the cognitive subscale of the AD Assessment Scale (ADAS-cog), and measures demonstrating clinical relevance, i.e. Clinician Interview-Based Impression of Change incorporating care-giver information (CIBIC-Plus) as a global measure and the Progressive Deterioration Scale (PDS) as a functional measure. In addition, the severity of disease was evaluated using the Mini-Mental State Examination (MMSE) and the Global Deterioration Scale (GDS) in both studies.^{14,15} These trials also included an indirect measure of behaviour in the Behavioral Pathology in AD (BEHAVE-AD), as a component of the CIBIC-Plus.¹⁸ In total, the two trials comprised 1,424 patients with mild to moderate probable AD who were randomised to oral rivastigmine (950 patients) or placebo (474 patients) for 26 weeks. In both trials, patients statistically significantly improved their scores on the ADAS-cog and the CIBIC-Plus after treatment with rivastigmine 6–12mg/day in comparison with placebo. *Table 1* shows important findings from these trials. Significant effects were also demonstrated on measures of ADL, as assessed by the PDS.^{14,15}

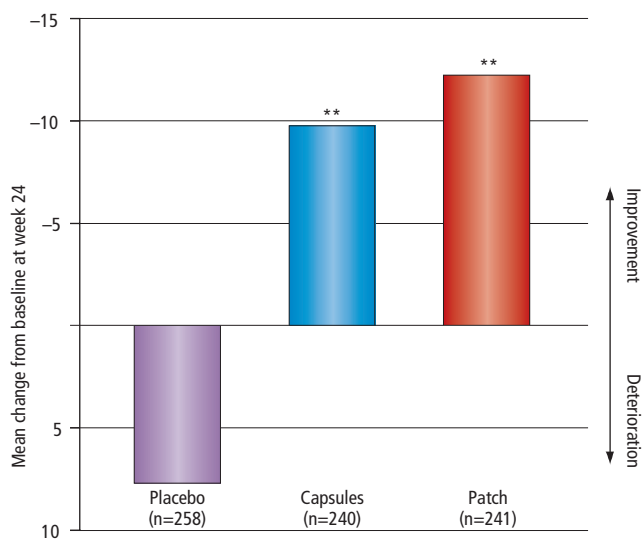
In a *post hoc* analysis of pooled BEHAVE-AD data from these two trials plus one other randomised, double-blind, placebo-controlled trial,¹⁹ significant improvements in paranoid and delusional ideation and aggressiveness were revealed after treatment for 26 weeks with rivastigmine ($p=0.002$) compared with placebo ($p=0.046$) in patients with behavioural and psychological symptoms at baseline.¹⁸

The most common adverse events recorded in these studies were nausea and vomiting (see *Table 2*). It should be noted that these early trials of rivastigmine capsules used forced, rapid titration of rivastigmine, with two-week intervals between titration steps.^{14,15} Subsequently, it has been described that rates of these events may be reduced with slower dose titration,²⁰ as may other measures that reduce and prolong the maximum observed plasma concentration (C_{max}) and the time at which C_{max} is attained (t_{max}), respectively, such as administering the medication with food or via transdermal patch delivery.²¹

Rivastigmine Patch

The IDEAL (Investigation of transDermal Exelon in Alzheimer's disease) study was a 24-week double-blind, double-dummy, placebo- and active-controlled trial comparing the efficacy, safety and tolerability of rivastigmine patches with capsules and placebo.^{16,17} A total of 1,195 AD patients were randomised to placebo or one of three target dose groups: 9.5mg/24-hour rivastigmine patch, 17.4mg/24-hour rivastigmine patch or 12mg/day rivastigmine capsules. Primary efficacy measures were the

Figure 1: Mean Changes from Baseline at 24 Weeks with Rivastigmine and Placebo on Trail Making Test A Scores



**p<0.001 versus placebo

Mean changes from baseline with placebo, 3–12mg/day rivastigmine capsules and 9.5mg/24-hour rivastigmine patch on Trail Making Test A scores at week 24 of the Investigation of transDermal Exelon in Alzheimer's disease (IDEAL) study.¹⁶ Intent-to-treat last observation carry-forward (ITT-LOCF) patients with valid baseline and week 24 scores. p-values derived from two-way analysis of covariance (ANCOVA) using treatment, country and baseline scores as explanatory variables, and based on least-square mean comparisons of each rivastigmine group versus placebo.

ADAS-cog and the AD Cooperative Study – Clinical Global Impression of Change (ADCS-CGIC), while secondary outcome measures assessed a range of aspects, including ADL, behaviour (as assessed by the Neuropsychiatric Inventory [NPI]) and executive function. For the purposes of this article, only the data from regulatory authority-approved target dose rivastigmine 9.5mg/24-hour patch will be considered with the active (rivastigmine capsules) and placebo control groups. Patients treated with the 9.5mg/24-hour rivastigmine patch or 12mg/day rivastigmine capsules showed significant improvements over placebo with respect to ADAS-cog and ADCS-CGIC (see Table 1).^{16,17} There were also significant improvements in both groups versus placebo on measures of ADL and the MMSE. The Trail Making Test Part A (TMT-A), which assesses attention, visual tracking and motor processing speed, also showed significant improvements in patients treated with rivastigmine versus those given placebo (both p<0.001) (see Figure 1). Changes from baseline were not significant versus placebo on the NPI, though there was a trend towards improvement in both groups.

Consistent with the pharmacokinetic rationale for developing the patch, the IDEAL study showed that the 9.5mg/24-hour rivastigmine patch provided comparable efficacy to highest dose capsules. Adverse events such as nausea and vomiting were substantially reduced with the 9.5mg/24-hour rivastigmine patch compared with capsules. Incidences of nausea and vomiting were three times fewer with the patch than with capsules (7.2 and 6.2% for the patch versus 23.1 and 17% for capsules for nausea and vomiting, respectively)^{16,17} (see Table 2).

Direct comparisons between individual trials do not allow firm conclusions. However, in Table 1 it is apparent that the magnitude of the effects of treatment with a rivastigmine patch in the IDEAL trial was smaller for the majority of comparable outcome measures than the

treatment effects of rivastigmine oral observed in the earlier trials. However, the benefits of treatment with rivastigmine oral up to 12mg/day were also reduced in this study¹⁶ in comparison with the initial clinical trials of rivastigmine.^{14,15} The rate of decline of patients given placebo was also considerably less in the IDEAL trial. These observations are thought to be the result of factors relating to evolving study population profiles.¹⁷ In summary, pivotal trials of rivastigmine oral and rivastigmine patch demonstrated that target doses of oral rivastigmine (6–12mg/day) and rivastigmine patch (9.5mg/24-hour) provide significant efficacy versus placebo on measures of cognition, global status and ADL.^{14–16}

Rivastigmine in Parkinson's Disease Dementia

In 2005, rivastigmine became the first treatment to be approved for PDD, based on the results of a large clinical trial including patients recruited from 11 countries in Europe and Canada,²² and remains the only treatment approved for this indication. A total of 541 patients with mild to moderate dementia that developed at least two years after they were diagnosed with PD were given rivastigmine oral (3–12mg/day) or placebo for 24 weeks. Rivastigmine demonstrated significant efficacy versus placebo on all primary and secondary efficacy variables, which were chosen based on their clinical relevance in this population.²²

Rivastigmine-treated patients showed an improvement in cognition as measured by mean change in ADAS-cog from baseline compared with a deterioration in patients given placebo (p<0.001). Significantly more patients treated with rivastigmine had a favourable outcome compared with placebo-treated patients in the global assessment using the ADCS-CGIC scale (p<0.05). Analysis of the secondary efficacy variables (which included the ADCS-ADL for activities of daily living, 10-item NPI for behavioural symptoms, computerised tests for attention, clock drawing and verbal fluency tests as measures of executive functions and MMSE) revealed that rivastigmine provided significant benefits over placebo on all of these measures (see Table 3).²² The most common adverse events were nausea (reported by 29% of rivastigmine-treated patients and 11.2% of the placebo-treated group; p<0.001) and vomiting (reported by 16.6 and 1.7% of rivastigmine- and placebo-treated patients, respectively; p<0.001). Tremor was reported as an adverse event in 10.2% of patients in the rivastigmine and 3.9% of patients in the placebo group (p=0.01), but was so severe as to cause discontinuation from the study in only 1.7% of patients treated with rivastigmine.²²

An in-depth review of safety data associated with this trial,²³ and a subsequent 24-week open-label extension in which all patients remaining in the study were treated with rivastigmine,²⁴ suggested that while the initial exposure to rivastigmine may transiently increase the incidence of tremor, rivastigmine treatment did not significantly worsen parkinsonian symptoms.²³ There was no evidence of adverse long-term motor outcomes during the open-label extension phase, and no new safety concerns arose during the trial.²³ During the 24-week double-blind study, there were fewer deaths with rivastigmine than with placebo (1.1 versus 3.9%).^{22,25}

Rivastigmine in Subpopulations

In AD patients, the features associated with a more rapid disease course may predict larger treatment differences between rivastigmine and placebo. For example, 20–40% of patients with AD experience hallucinations, which are reported to predict a more aggressive disease course.^{26,27} AD patients with hallucinations have been found to draw larger treatment benefits from rivastigmine capsules compared with placebo. A recent meta-analysis of the

Table 3: Mean Changes from Baseline at 24 Weeks with Rivastigmine and Placebo on Major Outcome Measures in Parkinson's Disease Dementia²²

	ADAS-cog	ADCS-CGIC	ADCS-ADL	MMSE	NPI-10
Rivastigmine 3–12mg/day	-2.1±8.2** (n=329)	-0.2±1.4* (n=329)	-1.1±12.6* (n=333)	0.8±3.8* (n=335)	-2±10* (n=334)
Placebo	0.7±7.5 (n=161)	0.3±1.5 (n=165)	-3.6±10.3 (n=165)	-0.2±3.5 (n=166)	0.0±10.4 (n=166)

ADAS-cog = Alzheimer's Disease Assessment Scale – cognitive subscale; ADCS-CGIC = Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change; ADCS-ADL = Alzheimer's Disease Cooperative Study – Activities of Daily Living; MMSE = Mini-Mental State Examination; NPI-10 = 10-item Neuropsychiatric Inventory.

* = $p < 0.05$ versus placebo; ** $p < 0.001$ versus placebo.

Mean changes ± standard deviation. Negative mean changes on the ADAS-cog, ADCS-CGIC and NPI-10 scales indicate improvement. Negative mean changes on the ADCS-ADL and MMSE scales indicate deterioration.

data from the two major trials of rivastigmine oral reported that the subpopulation of AD patients with hallucinations at baseline showed a mean rivastigmine–placebo difference of 4.2 points ($p < 0.001$) on the ADAS-cog compared with 2.2 points in non-hallucinators ($p < 0.001$).²⁶ Similarly, a mean difference of 2.3 points ($p < 0.007$) on the PDS was seen in rivastigmine- versus placebo-treated patients without hallucinations at baseline, compared with a mean difference of 5.3 points ($p = 0.003$) in those patients with hallucinations at baseline.²⁶

In a large sample study over two years of 994 AD patients randomised to either rivastigmine or donepezil (Aricept®, Pfizer),²⁸ which compared the effects of the two agents, there were no significant differences between the two treatment groups in terms of primary outcome measures. However, *post hoc* analyses of subpopulations revealed some differences.^{29,30} Patients with AD who are carriers of the wild-type BuChE allele have an increased rate of disease progression in comparison with patients with the BuChE-K variant of the allele, the possession of which results in lower BuChE expression.³¹ Symptoms suggestive of concomitant Lewy body pathology, such as the presence of extrapyramidal symptoms,³² may also be associated with a poorer prognosis.³⁰ Retrospective analyses investigating patients exhibiting these factors found differential responses to treatment with rivastigmine in comparison with donepezil.^{29,30} An analysis of treatment response according to BuChE status²⁹ found that while patients with the BuChE-K variant declined to a similar extent on all efficacy measures over two years – regardless of whether they were treated with rivastigmine or donepezil – the decline in BuChE wild-type patients was greater in patients treated with donepezil compared with those treated with rivastigmine.²⁹ Significantly greater mean treatment responses to rivastigmine versus donepezil were seen in patients with the wild-type BuChE allele on several measures of efficacy, including the Severe Impairment Battery (SIB), ADCS-ADL, NPI and GDS (all $p < 0.05$).²⁹ There were no treatment differences in patients with the BuChE-K allele. Likewise, AD patients exhibiting symptoms suggestive of Lewy body pathology treated with rivastigmine were found to perform significantly better than those patients treated with donepezil on efficacy measures including the SIB, MMSE and ADSC-ADL (all $p < 0.05$).

Similarly, in PDD patients the presence of hallucinations at baseline has been reported to be associated with larger rivastigmine–placebo treatment differences: patients with visual hallucinations at baseline tend to have greater treatment benefits compared with placebo on measures of cognition and behaviour than non-hallucinators.³³ On the ADAS-cog, PDD patients with hallucinations at baseline declined by 2.1 points compared with a 0.1-point improvement for non-hallucinators.³³ Similarly, retrospective analysis of patients in the two AD studies revealed a 3.7-point decline on the ADAS-cog in patients with hallucinations versus a 2.5-point decline in non-hallucinators. Driven mainly by the greater placebo

decline in the hallucinating subpopulation, rivastigmine–placebo differences on the ADCS-ADL in PDD patients with visual hallucinations at baseline tended to be larger than for non-hallucinators. Another *post hoc* analysis suggested that patients with elevated levels of plasma homocysteine – a measure associated with cognitive decline in the elderly³⁴ – have a greater response to rivastigmine than patients with normal or low plasma homocysteine, as assessed by measures of cognition and global change.³⁵

Commentary on Rivastigmine in Alzheimer's and Parkinson's Disease Dementias

A recent review by the author compared treatment responses to rivastigmine in patients with AD and PDD as well as its tolerability and safety,²⁶ based on data from two large randomised clinical trials conducted in AD^{14,15} and one in PDD.²² Over six months of treatment, the effects of rivastigmine versus placebo on cognitive performance were quantitatively similar in AD and PDD patients. Qualitatively, PDD patients showed an improvement from baseline at the end of six months, whereas AD patients showed a stabilisation at baseline values after initial improvement.²⁶ Treatment responses to rivastigmine on measures of ADL (the PDS in the AD studies and the ADCS-ADL in the PDD trial) were also quantitatively similar in both forms of dementia, reflecting a stabilisation of symptoms rather than an overall improvement.²⁶

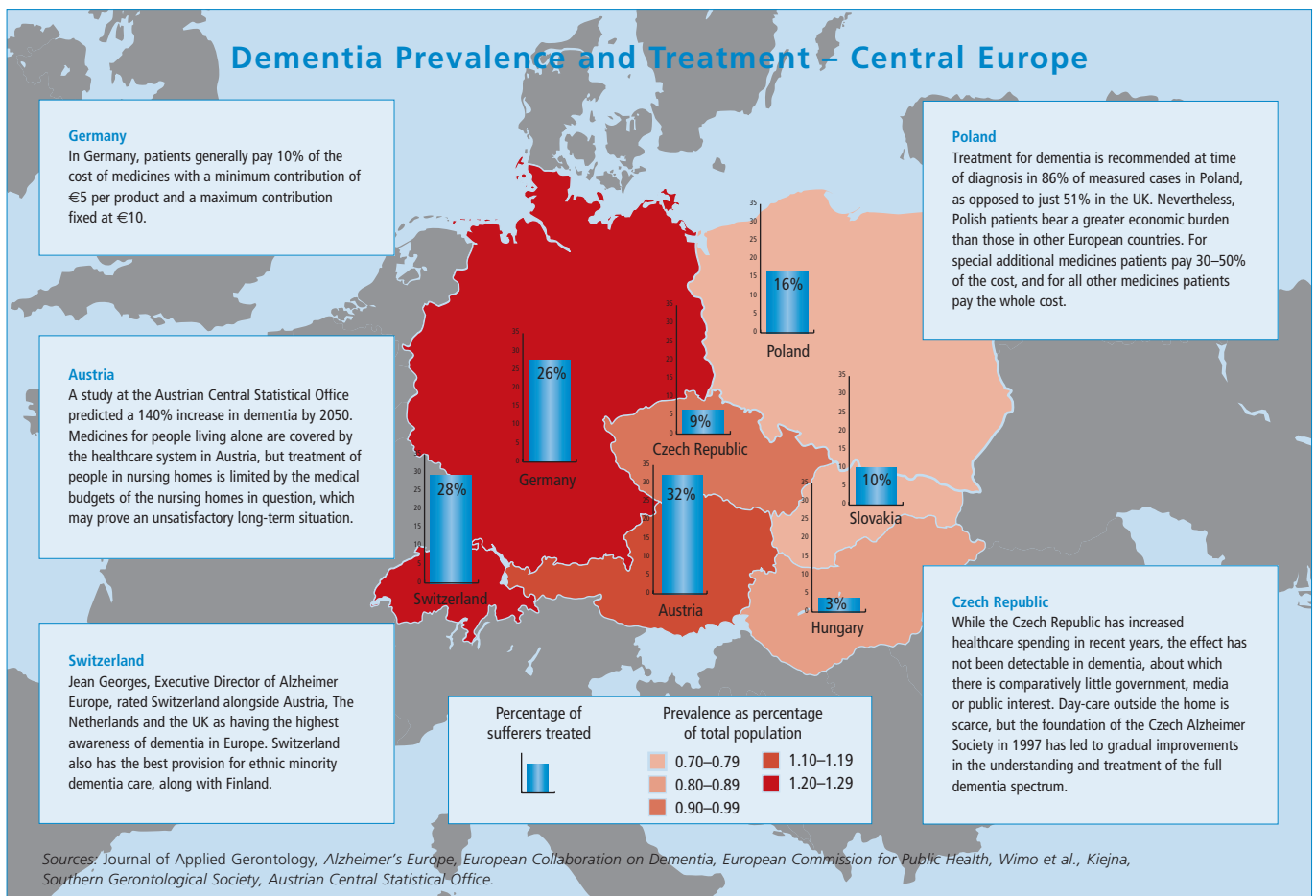
The subpopulations of placebo-treated patients with hallucinations at baseline showed a particularly rapid decline in both the AD and PDD studies. Greater treatment differences (rivastigmine versus placebo) were seen in the subpopulations of both PDD and AD patients with hallucinations at baseline on measures of cognition, behaviour and global change.²⁶ Thus, in both populations hallucinations may identify patients who are likely to draw more benefit from treatment. This may be a reflection of the greater cortical cholinergic deficits and more rapid cognitive and functional decline associated with the presence of visual hallucinations in these patients.^{26,33}

Overall safety and adverse event profiles were comparable in AD and PDD patients. Nausea and vomiting were the most commonly reported adverse events for both populations receiving rivastigmine capsules,²⁶ whereby these adverse events appeared to be reduced in AD patients receiving the novel rivastigmine patch.¹⁷ Interestingly, PDD patients with visual hallucinations have been reported to show a better overall tolerability and achieve titration to higher doses of rivastigmine than patients without hallucinations.^{26,33} ■

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Transforming treatment for Alzheimer's dementia with a once-daily patch¹



ABBREVIATED PRESCRIBING INFORMATION

Exelon® 4.6 mg/24 h transdermal patch
Exelon® 9.5 mg/24 h transdermal patch

Indication: Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Presentations:** Transdermal patches delivering 4.6mg/24h or 9.5mg/24h rivastigmine. Each 4.6mg/24h patch (5cm²) contains 9mg of rivastigmine and delivers a dose of 4.6mg over 24h. Each 9.5mg/24h patch (10cm²) contains 18mg of rivastigmine and delivers a dose of 9.5mg over 24h. **Dosage and Administration:** Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's disease (AD). A caregiver should be available to regularly administer and monitor the treatment. Initial dose is 4.6mg/24h transdermal patch applied once daily. After a minimum of four weeks if treatment is well tolerated this dose should be increased to 9.5mg/24h transdermal patch, which is the recommended effective dose. This recommended maintenance dose can be continued for as long as the patient is deriving therapeutic benefit. Treatment should be temporarily interrupted if gastrointestinal adverse effects are observed until these adverse effects resolve. Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than several days. Otherwise treatment should be re-initiated with 4.6mg/24h. The transdermal patches should be applied once a day, at about the same time every day, to clean, dry, hairless, intact, healthy skin on the upper or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing. It is not recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine observed when the transdermal patch is applied to these areas of the body. The transdermal patch should not be applied to skin that is red, irritated or cut and should not be applied to the exact same area of skin within 14 days. **If switching from an oral dose of rivastigmine:** a patient on a dose of 3 mg/day oral rivastigmine can be switched to 4.6 mg/24h transdermal patches; a patient on a dose of 6 mg/day oral rivastigmine can be switched to 4.6 mg/24h transdermal patches; a patient on a stable and well tolerated dose of 9 mg/day oral rivastigmine can be switched to 9.5 mg/24h transdermal patches; if the oral dose of 9 mg/day has not been stable and well tolerated, a switch to 4.6 mg/24 h transdermal patches is recommended; a patient on a dose of 12 mg/day oral rivastigmine can be switched to 9.5 mg/24h transdermal patches. The first transdermal patch should be applied on the day following the last oral dose. **Contraindications:** Hypersensitivity to the active substance, to other carbamate derivatives or to any excipients used in the formulation. **Special Warnings & Precautions for use:** The incidence and severity of adverse events generally increase with increasing doses, particularly at dose changes. If treatment is interrupted for more than several days, it should be re-initiated with 4.6 mg/24h. Gastrointestinal disorders such as nausea and vomiting are dose-related, and may occur when initiating treatment and/or increasing the dose. Monitor bodyweight during therapy. Use with care in patients with sick sinus syndrome, conduction defects (sino-atrial block, atrio-ventricular block), active gastric or duodenal ulcers (or patients predisposed to these conditions), history of asthma or obstructive pulmonary disease and those predisposed to urinary obstruction and seizures. Rivastigmine may exacerbate or induce extrapyramidal symptoms. Avoid eye contact after handling. Patients with bodyweight <50kg and patients with clinically significant hepatic impairment may experience more adverse events. **Pregnancy and Lactation:** Exelon transdermal patch should not be used in pregnancy unless strictly necessary. Women receiving Exelon

should not breastfeed. **Interactions:** May exaggerate effects of succinylcholine-type muscle relaxants during anaesthesia. Do not give with cholinomimetic drugs. May interfere with activity of anticholinergic medications. No interactions were observed with digoxin, warfarin, diazepam or fluoxetine in studies of healthy volunteers. Metabolic drug interactions unlikely, although may inhibit butyrylcholinesterase-mediated metabolism of other drugs. **Undesirable Effects:** Most commonly reported adverse drug reactions are gastrointestinal, including nausea (7.2% with 9.5mg/24h) and vomiting (6.2% with 9.5mg/24h). The following adverse reactions have been reported with Exelon transdermal patch. *Common* (>1/100, <1/10): urinary tract infection, anorexia, anxiety, depression, delirium, headache, syncope, nausea, vomiting, diarrhoea, dyspepsia, abdominal pain, rash, application site skin reactions (e.g. application site erythema, application site pruritus, application site oedema, application site dermatitis, application site irritation), asthenic conditions (e.g. fatigue, asthenia), pyrexia, weight decreased. *Uncommon* (>1/1,000, <1/100): Bradycardia, gastric ulcer. *Very rare* (<1/10,000): Extrapyramidal symptoms. Prescribers should consult the Summary of Product Characteristics for full information regarding side-effects. **Package Quantities and price:** Basic NHS Prices (excluding VAT): 4.6mg/24h transdermal patch x 30 : £83.84 ; 9.5mg/24h transdermal patch x 30 : £83.84 **Legal Category:** POM. **Marketing authorisation number:** Exelon 4.6 mg/24 h transdermal patch:EU/1/98/066/019 - 022; Exelon 9.5 mg/24 h transdermal patch:EU/1/98/066/023 - 026. **Date of last revision of prescribing information:** September 2007.

Full prescribing information is available from: Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR. Telephone: (01276) 692255, Fax: (01276) 692508.

Information about adverse event reporting can be found at <http://www.yellowcard.gov.uk>. Adverse events should also be reported directly to Novartis Pharmaceuticals UK Ltd on 01276 698370.

Reference: 1. Exelon 4.6 mg/24h and 9.5 mg/24h transdermal patch Summary of Product Characteristics, September 2007. EXE08000029

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