SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Rivastigmine 6 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 6 mg.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard

Rivastigmine 6 mg:
Hard capsule with opaque red cap and opaque orange body, size “2”, which contain off white to slightly yellow powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of mild to moderately severe Alzheimer’s dementia.

Symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson’s disease.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer’s dementia or dementia associated with Parkinson’s disease. Diagnosis should be made according to current guidelines. Therapy with rivastigmine should only be started if a caregiver is available who will regularly monitor intake of the medicinal product by the patient.

Posology

Rivastigmine should be administered twice a day, with morning and evening meals. The capsules should be swallowed whole.

Initial dose
1.5 mg twice a day.

Dose titration
The starting dose is 1.5 mg twice a day. If this dose is well tolerated after a minimum of two weeks of treatment, the dose may be increased to 3 mg twice a day. Subsequent increases to 4.5 mg and then 6 mg twice a day should also be based on good tolerability of the current dose and may be considered after a minimum of two weeks of treatment at that dose level.

If adverse reactions (e.g. nausea, vomiting, abdominal pain or loss of appetite), weight decrease or worsening of extrapyramidal symptoms (e.g. tremor) in patients with dementia associated with Parkinson's disease are observed during treatment, these may respond to omitting one or more doses. If adverse reactions persist, the daily dose should be temporarily reduced to the previous well-tolerated dose or the treatment may be discontinued.

Maintenance dose
The effective dose is 3 to 6 mg twice a day; to achieve maximum therapeutic benefit patients should be maintained on their highest well tolerated dose**.** The recommended maximum daily dose is 6 mg twice a day.

Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of rivastigmine should be reassessed on a regular basis, especially for patients treated at doses less than 3 mg twice a day. If after 3 months of maintenance dose treatment the patient's rate of decline in dementia symptoms is not altered favourably, the treatment should be discontinued. Discontinuation should also be considered when evidence of a therapeutic effect is no longer present.

Individual response to rivastigmine cannot be predicted. However, a greater treatment effect was seen in Parkinson's disease patients with moderate dementia. Similarly a larger effect was observed in Parkinson's disease patients with visual hallucinations (see section 5.1).

Treatment effect has not been studied in placebo-controlled trials beyond 6 months.

Re-initiation of therapy
If treatment is interrupted for more than three days, it should be re-initiated at 1.5 mg twice daily. Dose titration should then be carried out as described above.

Renal and hepatic impairment
No dose adjustment is necessary for patients with mild to moderate renal or hepatic impairment. However, due to increased exposure in these populations dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant renal or hepatic impairment might experience more adverse reactions. Patients with severe hepatic impairment have not been studied, however, Rivastigmine capsules may be used in this patient population provided close monitoring is exercised (see sections 4.4 and 5.2).

Paediatric population

There is no relevant use of rivastigmine in the paediatric population in the treatment of Alzheimer's disease.

4.3 Contraindications

The use of this medicinal product is contraindicated in patients with known hypersensitivity to the active substance rivastigmine, to other carbamate derivatives or to any of the excipients listed in section 6.1.

Previous history of application site reactions suggestive of allergic contact dermatitis with rivastigmine patch (see section 4.4).

4.4 Special warnings and precautions for use

The incidence and severity of adverse reactions generally increase with higher doses. If treatment is interrupted for more than three days, it should be re-initiated at 1.5 mg twice daily to reduce the possibility of adverse reactions (e.g. vomiting).

Skin application site reactions may occur with rivastigmine patch and are usually mild or moderate in intensity. These reactions are not in themselves an indication of sensitisation. However, use of rivastigmine patch may lead to allergic contact dermatitis.

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see section 4.3).

Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

There have been rare post-marketing reports of patients experiencing allergic dermatitis (disseminated) when administered rivastigmine irrespective of the route of administration (oral, transdermal). In these cases, treatment should be discontinued (see section 4.3).

Patients and caregivers should be instructed accordingly.

Dose titration: Adverse reactions (e.g. hypertension and hallucinations in patients with Alzheimer's dementia and worsening of extrapyramidal symptoms, in particular tremor, in patients with dementia associated

with Parkinson's disease) have been observed shortly after dose increase. They may respond to a dose reduction. In other cases, rivastigmine has been discontinued (see section 4.8).

Gastrointestinal disorders such as nausea, vomiting and diarrhoea are dose related, and may occur particularly when initiating treatment and/or increasing the dose (see section 4.8). These adverse reactions occur more commonly in women. Patients who show signs or symptoms of dehydration resulting from prolonged vomiting or diarrhoea can be managed with intravenous fluids and dose reduction or discontinuation if recognised and treated promptly. Dehydration can be associated with serious outcomes.

Patients with Alzheimer's disease may lose weight. Cholinesterase inhibitors, including rivastigmine, have been associated with weight loss in these patients. During therapy patient's weight should be monitored.

In case of severe vomiting associated with rivastigmine treatment, appropriate dose adjustments as recommended in section 4.2 must be made. Some cases of severe vomiting were associated with oesophageal rupture (see section 4.8). Such events appeared to occur particularly after dose increments or high doses of rivastigmine.

Electrocardiogram QT prolongation may occur in patients treated with certain cholinesterase inhibitor products including rivastigmine. Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients with pre-existing, or a family history of, QTc prolongation or at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes. Clinical monitoring (ECG) may also be required (see sections 4.5 and 4.8).

Care must be taken when using rivastigmine in patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see section 4.8).

Rivastigmine may cause increased gastric acid secretions. Care should be exercised in treating patients with active gastric or duodenal ulcers or patients predisposed to these conditions.

Cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

Cholinomimetics may induce or exacerbate urinary obstruction and seizures. Caution is recommended in treating patients predisposed to such diseases.

The use of rivastigmine in patients with severe dementia of Alzheimer's disease or associated with Parkinson's disease, other types of dementia or other types of memory impairment (e.g. age-related cognitive decline) has not been investigated and therefore use in these patient populations is not recommended.

Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening (including bradykinesia, dyskinesia, gait abnormality) and an increased incidence or severity of tremor have been observed in patients with dementia associated with Parkinson's disease (see section 4.8). These events led to the discontinuation of rivastigmine in some cases (e.g. discontinuations due to tremor 1.7% on rivastigmine vs 0% on placebo). Clinical monitoring is recommended for these adverse reactions.

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. However, rivastigmine may be used in this patient population and close monitoring is necessary.

Patients with body weight below 50 kg may experience more adverse reactions and may be more likely to discontinue due to adverse reactions.

4.5 Interaction with other medicinal products and other forms of interaction

As a cholinesterase inhibitor, rivastigmine may exaggerate the effects of succinylcholine-type muscle relaxants during anaesthesia. Caution is recommended when selecting anaesthetic agents. Possible dose adjustments or temporarily stopping treatment can be considered if needed.

In view of its pharmacodynamic effects and possible additive effects, rivastigmine should not be given concomitantly with other cholinomimetic substances. Rivastigmine might interfere with the activity of anticholinergic medicinal products (e. g. oxybutynin, tolterodine).

Additive effects leading to bradycardia (which may result in syncope) have been reported with the combined use of various beta-blockers (including atenolol) and rivastigmine. Cardiovascular beta-blockers are expected to be associated with the greatest risk, but reports have also been received in patients using other beta-blockers. Therefore, caution should be exercised when rivastigmine is

combined with beta-blockers and also other bradycardia agents (e.g.class III antiarrhythmic agents, calcium channel antagonists, digitalis glycoside, pilocarpin).

Since bradycardia constitutes a risk factor in the occurrence of torsades de pointes, the combination of rivastigmine with QT prolongation or torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sultopride, amisulpride, tiapride, veralipride), pimozide, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacine should be observed with caution and clinical monitoring (ECG) may also be required.

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

According to its metabolism, metabolic interactions with other medicinal products appear unlikely, although rivastigmine may inhibit the butyrylcholinesterase mediated metabolism of other substances.

4.6 Pregnancy and lactation

Pregnancy

In pregnant animals, rivastigmine and/or metabolites crossed the placenta. It is not known if this occurs in humans. No clinical data on exposed pregnancies are available. In peri/postnatal studies in rats, an increased gestation time was observed. Rivastigmine should not be used during pregnancy unless clearly necessary.

Breast-feeding

In animals, rivastigmine is excreted into milk. It is not known if rivastigmine is excreted into human milk. Therefore, women on rivastigmine should not breast-feed.

Fertility

No adverse effects of rivastigmine were observed on fertility or reproductive performance in rats (see section 5.3). Effects of rivastigmine on human fertility are not known.

4.7 Effects on ability to drive and use machines

Alzheimer's disease may cause gradual impairment of driving performance or compromise the ability to use machinery. Furthermore, rivastigmine can induce dizziness and somnolence, mainly when initiating treatment or increasing the dose. As a consequence, rivastigmine has minor or moderate influence on the ability to drive and use machines. Therefore, the ability of patients with dementia on rivastigmine to continue driving or operating complex machines should be routinely evaluated by the treating physician.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions (ADRs) are gastrointestinal, including nausea (38%) and vomiting (23%), especially during titration. Female patients in clinical studies were found to be more susceptible than male patients to gastrointestinal adverse reactions and weight loss.

Tabulated list of adverse reactions

Adverse reactions in Table 1 and Table 2 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

The following adverse reactions, listed below in Table 1, have been accumulated in patients with Alzheimer's dementia treated with rivastigmine.

Table 1

Infections and infestations	
Very rare	Urinary infection
Metabolism and nutrition disorders	
Very common	Anorexia
Common	Decreased appetite
Not known	Dehydration
Psychiatric disorders	
Common	Nightmares
	Agitation
	Confusion
	Anxiety
Uncommon	Insomnia
	Depression
Very rare	Hallucinations
Not known	Aggression
	Restlessness
Nervous system disorders	
Very common	Dizziness
Common	Headache
	Somnolence
	Tremor
Uncommon	Syncope
Rare	Seizures
Not known	Pleurothotonus (Pisa syndrome)
Very rare	Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders	
Rare	Angina pectoris
Very rare	Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia)
Not known	Sick sinus syndrome
Vascular disorders	
Very rare	Hypertension
Gastrointestinal disorders	

Very common	Nausea
	Vomiting
	Diarrhoea
Common	Abdominal pain and dyspepsia
Rare	Gastric and duodenal ulcers
Very rare	Gastrointestinal haemorrhage
	Pancreatitis
Not known	Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Hepatobiliary disorders	
Uncommon	Elevated liver function tests
Not known	Hepatitis
Skin and subcutaneous tissue disorders	
Common	Hyperhydrosis
Rare	Rash
Not known	Pruritus, allergic dermatitis (disseminated)
General disorders and administration site conditions	
Common	Fatigue and asthenia
	Malaise
Uncommon	Fall
Investigations	
Common	Weight loss

The following additional adverse reactions have been observed with rivastigmine transdermal patches: delirium, pyrexia, decreased appetite, urinary incontinence (common), psychomotor hyperactivity (uncommon), erythema, urticaria, vesicles, allergic dermatitis (not known).

Table 2 shows the adverse reactions reported during clinical studies conducted in patients with dementia associated with Parkinson's disease treated with rivastigmine capsules.

Table 2

Metabolism and nutritional disorders	
Common	Decreased appetite
	Dehydration
Psychiatric disorders	
Common	Insomnia
	Anxiety
	Restlessness
	Hallucination, visual
	Depression
Not known	Aggression
Nervous system disorders	
Very common	Tremor
Common	Dizziness
	Somnolence
	Headache
	Parkinson's disease (worsening)
	Bradykinesia

	Dyskinesia
	Hypokinesia
	Cogwheel rigidity
Uncommon	Dystonia
Cardiac disorders	
Common	Bradycardia
Uncommon	Atrial Fibrillation
	Atrioventricular block
Not known	Sick sinus syndrome
Vascular disorders	
Common	Hypertension
Uncommon	Hypotension
Gastrointestinal disorders	
Very common	Nausea
	Vomiting
Common	Diarrhoea
	Abdominal pain and dyspepsia
	Salivary hypersecretion
Hepatobiliary disorders	
Not known	Hepatitis
Skin and subcutaneous tissue disorders	
Common	Hyperhydrosis
Not known	Allergic dermatitis (disseminated)
General disorders and administration site conditions	
Very common	Fall
Common	Fatigue and asthenia
	Gait abnormality
	Parkinson gait

The following additional adverse reaction has been observed in a study of patients with dementia associated with Parkinson's disease treated with Exelon transdermal patches: agitation (common).

Table 3 lists the number and percentage of patients from the specific 24-week clinical study conducted with rivastigmine in patients with dementia associated with Parkinson's disease with pre-defined adverse events that may reflect worsening of parkinsonian symptoms.

Table 3

Pre-defined adverse events that may reflect worsening of parkinsonian symptoms in patients with dementia associated with Parkinson's disease	**Rivastigmine n (%)**	**Placebo n (%)**
Total patients studied	362 (100)	179 (100)
Total patients with pre-defined AE(s)	99 (27.3)	28 (15.6)
Tremor	37 (10.2)	7 (3.9)
Fall	21 (5.8)	11 (6.1)
Parkinson`s disease (worsening)	12 (3.3)	2 (1.1)
Salivary hypersecretion	5 (1.4)	0
Dyskinesia	5 (1.4)	1 (0.6)

Parkinsonism	8 (2.2)	1 (0.6)
Hypokinesia	1 (0.3)	0
Movement disorder	1 (0.3)	0
Bradykinesia	9 (2.5)	3 (1.7)
Dystonia	3 (0.8)	1 (0.6)
Gait abnormality	5 (1.4)	0
Muscle rigidity	1 (0.3)	0
Balance disorder	3 (0.8)	2 (1.1)
Muscoloskeletal stiffness	3 (0.8)	0
Rigors	1 (0.3)	0
Motor dysfunction	1 (0.3)	0

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms

Most cases of accidental overdose have not been associated with any clinical signs or symptoms and almost all of the patients concerned continued rivastigmine treatment 24 hours after the overdose.

Cholinergic toxicity has been reported with muscarinic symptoms that are observed with moderate poisonings such as miosis, flushing, digestive disorders including abdominal pain, nausea, vomiting and diarrhoea, bradycardia, bronchospasm and increased bronchial secretions, hyperhidrosis, involuntary urination and/or defecation, lacrimation, hypotension and salivary hypersecretion.

In more severe cases nicotinic effects might develop such as muscular weakness, fasciculations, seizures and respiratory arrest with possible fatal outcome.

Additionally there have been post-marketing cases of dizziness, tremor, headache, somnolence, confusional state, hypertension, hallucinations and malaise.

Management

As rivastigmine has a plasma half-life of about 1 hour and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose no further dose of rivastigmine should be administered for the next 24 hours. In overdose accompanied by severe nausea and vomiting, the use of antiemetics should be considered. Symptomatic treatment for other adverse reactions should be given as necessary.

In massive overdose, atropine can be used. An initial dose of 0.03 mg/kg intravenous atropine sulphate is recommended, with subsequent doses based on clinical response. Use of scopolamine as an antidote is not recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anticholinesterases, ATC code: N06DA03

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. In healthy young men, an oral 3 mg dose decreases acetylcholinesterase (AChE) activity in CSF by approximately 40% within the first 1.5 hours after administration. Activity of the enzyme returns to baseline levels about 9 hours after the maximum inhibitory effect has been achieved. In patients with Alzheimer's disease, inhibition of AChE in CSF by rivastigmine was dose-dependent up to 6 mg given twice daily, the highest dose tested. Inhibition of butyrylcholinesterase activity in CSF of 14 Alzheimer patients treated by rivastigmine was similar to that of AChE.

<u>Clinical studies in Alzheimer's dementia</u>

The efficacy of rivastigmine has been established through the use of three independent, domain specific, assessment tools which were assessed at periodic intervals during 6 month treatment periods. These include the ADAS- Cog (Alzheimer's Disease Assessment Scale - Cognitive subscale, a performance based measure of cognition), the CIBIC-Plus (Clinician's Interview Based Impression of Change-Plus, a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the PDS (Clinician's Interview Based Impression of Change-Plus, a caregiver-rated assessment of the activities of daily living including personal hygiene, feeding, dressing, household chores such as shopping, retention of ability to orient oneself to surroundings as well as involvement in activities relating to finances, etc.).

The patients studied had an MMSE (Mini-Mental State Examination) score of 10–24.

The results for clinically relevant responders pooled from two flexible dose studies out of the three pivotal 26-week multicentre studies in patients with mild-to-moderately severe Alzheimer's Dementia, are provided in Table 4 below. Clinically relevant improvement in these studies was defined a priori as at least 4-point improvement on the ADAS-Cog, improvement on the CIBIC- Plus, or at least a 10% improvement on the PDS.

In addition, a post-hoc definition of response is provided in the same table. The secondary definition of response required a 4-point or greater improvement on the ADAS-Cog, no worsening on the CIBIC-Plus, and no worsening on the PDS. The mean actual daily dose for responders in the 6–12 mg group, corresponding to this definition, was 9.3 mg. It is important

to note that the scales used in this indication vary and direct comparisons of results for different therapeutic agents are not valid.

Table 4

	Patients with Clinically Significant Response (%)			
	Intent to Treat		**Last Observation Carried Forward**	
Response Measure	**Rivastigmine 6–12 mg N=473**	**Placebo N=472**	**Rivastigmine 6–12 mg N=379**	**Placebo N=444**
ADAS-Cog: improvement of at least 4 points	21***	12	25***	12
CIBIC-Plus: improvement	29***	18	32***	19
PDS: improvement of at least 10%	26***	17	30***	18
At least 4 points improvement on ADASCog with no worsening on CIBIC-Plus and PDS	10*	6	12**	6

*p<0.05, **p<0.01, ***p<0.001

Clinical studies in dementia associated with Parkinson's disease

The efficacy of rivastigmine in dementia associated with Parkinson's disease has been demonstrated in a 24-week multicentre, double-blind, placebo- controlled core study and its 24-week open-label extension phase. Patients involved in this study had an MMSE (Mini-Mental State Examination) score of 10–24. Efficacy has been established by the use of two independent scales which were assessed at regular intervals during a 6-month treatment period as shown in Table 5 below: the ADAS-Cog, a measure of cognition, and the global measure ADCS-CGIC (Alzheimer's Disease Cooperative Study- Clinician's Global Impression of Change).

Table 5

Dementia associated with Parkinson's Disease	**ADAS-Cog Rivastigmine**	**ADAS-Cog Placebo**	**ADCS-CGIC Rivastigmine**	**ADCS-CGIC Placebo**
ITT + RDO population	(n=329)	(n=161)	(n=329)	(n=165)
Mean baseline ± SD	23.8 ± 10.2	24.3 ± 10.5	n/a	n/a
Mean change at 24 weeks ± SD	**2.1 ± 8.2**	-0.7 ± 7.5	**3.8 ± 1.4**	4.3 ± 1.5
Adjusted treatment difference	2.88[1]		n/a	
p-value versus placebo	<0.001[1]		0.007[2]	
ITT - LOCF population	(n=287)	(n=154)	(n=289)	(n=158)
Mean baseline ± SD	24.0 ± 10.3	24.5 ± 10.6	n/a	n/a
Mean change at 24 weeks ± SD	**2.5 ± 8.4**	-0.8 ± 7.5	**3.7 ± 1.4**	4.3 ± 1.5
Adjusted treatment difference	3.54[1]		n/a	
p-value versus placebo	<0.001[1]		<0.001[2]	

[1] Based on ANCOVA with treatment and country as factors and baseline ADAS-Cog as a covariate. A positive change indicates improvement.
[2] Mean data shown for convenience, categorical analysis performed using van Elteren test
ITT: Intent-To-Treat; RDO: Retrieved Drop Outs; LOCF: Last Observation Carried Forward

Although a treatment effect was demonstrated in the overall study population, the data suggested that a larger treatment effect relative to placebo was seen in the subgroup of patients with moderate dementia associated with Parkinson's disease. Similarly a larger treatment effect was observed in those patients with visual hallucinations (see Table 6).

Table 6

Dementia associated with Parkinson's Disease	**ADAS-Cog Rivastigmine**	**ADAS-Cog Placebo**	**ADAS-Cog Rivastigmine**	**ADAS-Cog Placebo**
	Patients with visual hallucinations		**Patients without visual hallucinations**	
ITT + RDO population	(n=107)	(n=60)	(n=220)	(n=101)
Mean baseline ± SD Mean change at 24 weeks ± SD	25.4 ± 9.9 **1.0 ± 9.2**	27.4 ± 10.4 -2.1 ± 8.3	23.1 ± 10.4 **2.6 ± 7.6**	22.5 ± 10.1 0.1 ± 6.9
Adjusted treatment difference p-value versus placebo	4.27[1] 0.002[1]		2.09[1] 0.015[1]	
	Patients with moderate dementia (MMSE 10-17)		**Patients with mild dementia (MMSE 18-24)**	
ITT - LOCF population	(n=87)	(n=44)	(n=237)	(n=115)
Mean baseline ± SD Mean change at 24 weeks ± SD	32.6 ± 10.4 **2.6 ± 9.4**	33.7 ± 10.3 -1.8 ± 7.2	20.6 ± 7.9 **1.9 ± 7.7**	20.7 ± 7.9 -0.2 ± 7.5
Adjusted treatment difference p-value versus placebo	4.73[1] 0.002[1]		2.14[1] 0.010[1]	

[1] Based on ANCOVA with treatment and country as factors and baseline ADAS-Cog as a covariate. A positive change indicates improvement.
ITT: Intent-To-Treat; RDO: Retrieved Drop Outs

The European Medicines Agency has waived the obligation to submit the results of studies with rivastigmine in all subsets of the paediatric population in the treatment of Alzheimer's dementia and in the treatment of dementia in patients with idiopathic Parkinson's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. As a consequence of rivastigmine's interaction with its target enzyme, the increase in bioavailability is about 1.5-fold greater than that expected from the increase in dose. Absolute bioavailability after a 3 mg dose is about 36 % ± 13 %. Administration of rivastigmine with food delays absorption (t_{max}) by 90 min and lowers C_{max} and increases AUC by approximately 30 %.

Distribution

Protein binding of rivastigmine is approximately 40%. It readily crosses the blood brain barrier and has an apparent volume of distribution in the range of 1.8 - 2.7 l/kg.

Biotransformation

Rivastigmine is rapidly and extensively metabolised (half-life in plasma approximately 1 hour), primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. *In vitro*, this metabolite shows minimal inhibition of acetylcholinesterase (< 10 %).

Based on in vitro studies, no pharmacokinetic interaction is expected with medicinal products metabolised by the following cytochromes isoemzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6. Based on evidence from animal studies the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Total plasma clearance of rivastigmine was approximately 130 l/h after a 0.2 mg intravenous dose and decreased to 70 l/h after a 2.7 mg intravenous dose.

Elimination

Unchanged rivastigmine is not found in the urine; renal excretion of the metabolites is the major route of elimination. Following administration of ^{14}C-rivastigmine, renal elimination was rapid and essentially complete (> 90 %) within 24 hours. Less than 1 % of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease.

A population pharmacokinetic analysis showed that nicotine use increases the oral clearance of rivastigmine by 23 % in patients with Alzheimer's disease (n=75 smokers and 549 non-smokers) following rivastigmine oral capsule doses of up to 12 mg/day.

Older People

While 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.

Hepatic impairment

The C_{max} of rivastigmine was approximately 60 % higher and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects.

Renal impairment

C_{max} and AUC of rivastigmine were more than twice as high in subjects with moderate renal impairment compared with healthy subjects; however there were no changes in C_{max} and AUC of rivastigmine in subjects with severe renal impairment.

5.3 Preclinical safety data

Repeated-dose toxicity studies in rats, mice and dogs revealed only effects associated with an exaggerated pharmacological action. No target organ toxicity was observed. No safety margins to human exposure were achieved in the animal studies due to the sensitivity of the animal models used.

Rivastigmine was not mutagenic in a standard battery of *in vitro* and *in vivo* tests, except in a chromosomal aberration test in human peripheral lymphocytes at a dose 10^4 times the maximum clinical exposure. The *in vivo* micronucleus test was negative. The major metabolite NAP226-90 also did not show a genotoxic potential.

No evidence of carcinogenicity was found in studies in mice and rats at the maximum tolerated dose, although the exposure to rivastigmine and its metabolites was lower than the human exposure. When normalised to body surface area, the exposure to rivastigmine and its metabolites was approximately equivalent to the maximum recommended human dose of 12 mg/day; however, when compared to the maximum human dose, a multiple of approximately 6-fold was achieved in animals.

In animals, rivastigmine crosses the placenta and is excreted into milk. Oral studies in pregnant rats and rabbits gave no indication of teratogenic potential on the part of rivastigmine. In oral studies with male and female rats, no adverse effects of rivastigmine were observed on fertility or reproductive performance of either the parent generation or the offspring of the parents.

A mild eye/mucosal irritation potential of rivastigmine was identified in a rabbit study.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rivastigmine 6 mg
Capsule content:
Microcrystalline cellulose
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate

Capsule:
Gelatin
Yellow iron oxide (E172)
Red iron oxide (E172)
Titanium dioxide (E171)
Sodium laurilsulfate
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister of PVC/PVDC with aluminium lidding foil.

Rivastigmine is available in packages of 2, 4, 10, 14, 20, 28, 30, 50, 56, 60, 90, 98, 100, 112 and 120 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Torrent Pharma (UK) Ltd.
3rd Floor, Nexus Building,
4 Gatwick Road,
Crawley,
West Sussex,
RH10 9BG,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 36687/0124

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/08/2014

10 DATE OF REVISION OF THE TEXT

10/10/2025