Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rivastigmine 2mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains rivastigmine hydrogen tartrate equivalent to 2 mg rivastigmine base.
For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Oral solution.
Clear, yellow solution.

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.

Rivastigmine oral solution should be administered twice a day, with morning or evening meals. The prescribed amount of the solution should be withdrawn from the container using the oral dosing syringe supplied. Rivastigmine oral solution may be swallowed directly from the syringe. Rivastigmine oral solution and rivastigmine capsules may be interchanged at equal doses.

<u>Initial dose</u>

1.5 mg twice a day.

<u>Dose titration</u>

The starting dose is 1.5 mg twice a day. If this is well tolerated after a minimum of two weeks 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.

<u>Maintenance dose</u>

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 assessed on a regular basis, especially for patients treated at doses at 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 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 several 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 (see sections 4.4 and 5.2). Patients with severe liver impairment have not been studied (see section 4.3).

Paediatric population

The safety and efficacy of rivastigmine in children aged 0 to 18 years have not been established. No data are available.

There is no relevant use of rivastigmine in the paediatric population in children aged 0 to 18 years in the treatment of Alzheimer's dementia and dementia in patients with idiopathic Parkinson'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 used in the formulation.

Previous history of application site reaction 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 several 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 disseminated skin hypersensitivity reactions 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 particularly tremor, in patients with dementia associated with Parkinson's disease) have been observed shortly after dose increase. They may respond to 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 dose of rivastigmine.

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.

Rivastigmine oral solution contains sodium benzoate. Benzoic acid is a mild irritant to the skin, eyes and mucous membrane.

The use of rivastigmine in patients with severe dementia of Alzheimer's 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 has been observed in patients with dementia associated with Parkinson's (see section 4.8). These events led to discontinuation of rivastigmine in some cases (e.g. discontinuation due to tremor 1.7% on rivastigmine vs 0% on placebo). Clinical monitoring is recommended for these adverse reactions.

<u>Special populations</u>

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see section

4.2 and 5.2). Patients with severe hepatic impairment have not been studied. However, rivastigmine may be used in this 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, rivastigmine should not be given concomitantly with other cholinomimetic substances and might interfere with the activity of anticholinergic medicinal products.

No pharmacokinetics 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 Fertility, pregnancy and lactation

For rivastigmine no clinical data on exposed pregnancies are available. No effects on fertility or embryofoetal development were observed in rats and rabbits, except at doses related to maternal toxicity. In peri/postnatal studies in rats, an increased gestation time was observed. Rivastigmine should not be used during pregnancy unless clearly necessary.

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.

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 therapy to continue driving or operating complex machines should be routinely evaluated by the treating physician.

4.8 Undesirable effects

The most commonly reported adverse reactions 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.

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, ≤1/10); uncommon (≥ 1/1,000, ≤ 1/100); rare (≥ 1/10,000, ≤ 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 nutritional disorders	
Very common	Anorexia
Not known	Dehydration
Psychiatric disorders	
Common	Agitation
Common	Confusion
Common	Anxiety
Uncommon	Insomnia
Uncommon	Depression
Very rare	Hallucinations
Not known	Aggression, restlessness
Nervous system disorders	
Very common	Dizziness
Common	Headache
Common	Somnolence
Common	Tremor
Uncommon	Syncope
Rare	Seizures
Very rare	Extrapyramidial 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,
Very common	Vomiting
Very common	Diarrhoea
Common	Abdominal pain and dyspepsia
Rare	Gastro and duodenal ulcers
Very rare	Gastrointestinal haemorrhage
Very rare	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
General disorders and administration site conditions	
Common	Fatigue and asthenia,
Common	Malaise
Uncommon	Fall
Investigations	
Common	Weight loss

The following additional reactions have been observed with rivastigmine transdermal patches: anxiety, delirium and pyrexia (common).

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
Common	Dehydration
Psychiatric disorders	
Common	Insomnia
Common	Anxiety
Common	Restlessness
Common	Hallucination, visual
Common	Depression
Not known	Aggression
Nervous system disorders	
Very common	Tremor
Common	Dizziness
Common	Somnolence
Common	Headache
Common	Worsening of Parkinson's disease
Common	Bradykinesia
Common	Dyskinesia
Common	Hypokinesia
Common	Cogwheel rigidity
Uncommon	Dystonia
Cardiac disorders	
Common	Bradycardia
Uncommon	Atrial fibrillation
Uncommon	Atrioventricular block
Not known	Sick sinus syndrome
Vascular disorders	
Common	Hypertension
Uncommon	Hypotension
Gastrointestinal disorders	
Very common	Nausea
Very common	Vomiting
Common	Diarrhoea
Common	Abdominal pain and dyspepsia
Common	Salivary hypersecretion
Hepatobiliary disorders	
Not known	Hepatitis
Skin and subcutaneous tissue disorders	
Common	Hyperhydrosis
General disorders and administration site conditions	
Very common	Fall
Common	Fatigue and asthenia
Common	Gait disturbance
Common	Parkinson gait

The following additional adverse reactions have been observed in a study of patients with dementia associated with Parkinson's disease treated with rivastigmine transdermal patches: agitation, depression (common).

Table 3 lists the number and percentage of patients from a 24-week clinical study 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

Predefined 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 disorders	3 (0.8)	2 (1.1)
Musculoskeletal stiffness	3 (0.8)	0
Rigors	1 (0.3)	0
Motor dysfunction	1 (0.3)	0

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. Where symptoms have occurred, they include nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg of rivastigmine occurred in one case; following conservative management the patient fully recovered within 24 hours.

Treatment
As rivastigmine has a plasma half-life of about 1 hour and 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 dose based on clinical response. Use of scopolamine as an antidote is recommended.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anticholinesterases

ATC code: N06DA03

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholinesterase by functional intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated 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 cerebrospinal fluid (CSF) by approximately 40% within the first 1.5 hours after administration. Activity of the enzyme returns to baseline levels about 9 hours after the maximum inhibitory effect has been achieved. 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 of CSF of 14 Alzheimer patients treated by rivastigmine was similar to that of AChE.

Clinical studies in Alzheimer's dementia

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 (Progressive Deterioration Scale, 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 patient studied had an MMSE (Mini-Mental State Examination) score of 10 – 24.

The results of clinically relevant responders pooled from two flexible dose studies out of 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 as priori as at least 4-point improvement on the ADAS-Cog, improvement on the CIBIC-Plus, or at least 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 not 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 ADS-Cog with no worsening on	10*	6	12**	6

CIBIC-Plus and PDS				

* 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**	**ADAS-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-LCOF 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 large treatment effect relative to placebo was seen in the subgroup of patients with moderate dementia associated with Parkinson's disease. Similarly a large 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**	**DAS-Cog Placebo**
	Patients with visual hallucinations		**Patients without visual hallucinations**	
ITT + RDO population	n = 107	n = 60	n = 220	n = 101
Mean baseline ± SD	25.4 ± 9.9	27.4 ± 10.4	23.1 ± 10.4	22.5 ± 10.1
Mean change at 24 weeks ± SD	**1.0 ± 9.2**	-2.1 ± 8.3	**2.6 ± 7.6**	0.1 ± 6.9
Adjusted treatment difference	4.27[1]		2.09[1]	
p-value versus placebo	0.002[1]		0.015[1]	
	Patients with moderate dementia (MMSE 10 – 17)		**Patients with mild dementia (MMSE 18 – 24)**	
ITT + RDO population	n = 87	n = 44	n = 237	n = 115
Mean baseline ± SD	32.6 ± 10.4	33.7 ± 10.3	20.6 ± 7.9	20.7 ± 7.9
Mean change at 245 weeks ± SD	**2.6 ± 9.4**	-1.8 ± 7.2	**1.9 ± 7.7**	-0.2 ± 7.5
Adjusted treatment difference	4.73[1]		2.14[1]	
p-value versus placebo	0.002[1]		0.010[1]	

1 Based on ANCOVA with treatment and country as factors and baseline ADS-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 oral solution with food delays absorption (tmax) by 74 min ad lowers Cmax by 43% and increases AUC by approximately 9%.

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.

Metabolism
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 evidence from in vitro and animal studies the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Total plasma clearance of rivastigmine was approximately 130 l/h after a 0.2 mg intravenous dose and decreased to 70 l/h after a 2.7 mg intravenous dose.

Excretion
Unchanged rivastigmine is not found in the urine; renal excretion of the metabolites is the major route of elimination. Following administration of 14C-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.

Elderly subjects
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.

Subjects with hepatic impairment
The Cmax 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.

Subjects with renal impairment
Cmax 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 Cmax 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 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 104 times the maximum clinical exposure. The in vivo micronucleus test was negative.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E211)
Citric acid monohydrate
Sodium citrate dihydrate
Quinoline yellow (E104)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years.
Rivastigmine should be used within 1 month of first opening the bottle.

6.4 Special precautions for storage

Store below 25ºC. Do not refrigerate or freeze. Keep the container in the outer carton in order to protect from light. Store in an upright position.

6.5 Nature and contents of container

Type III amber glass 120 ml bottle with a child-resistant HDPE cap and an oral dosing syringe.

6.6 Special precautions for disposal and other handling

The prescribed amount of solution should be withdrawn from the bottle using the oral dosing syringe supplied.

7 MARKETING AUTHORISATION HOLDER

Beacon Pharmaceuticals Ltd
85 High Street
Tunbridge Wells
Kent TN1 1YG
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1312/13/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 27th January 2012

10 DATE OF REVISION OF THE TEXT

November 2012