ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 1.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 1.5 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

White cap imprinted with "R" & white body imprinted with "1.5"

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 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 the 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 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 hepatic impairment have not been studied (see section 4.4).

Children:
Rivastigmine is not recommended for use in children.

4.3 Contraindications

The use of this medicinal product is contraindicated in patients with
- hypersensitivity to the active substance, other carbamate derivatives or to any of the excipients used in the formulation,

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).

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.

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). Patients with severe hepatic impairment have not been studied. However, Rivastigmine Teva 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, rivastigmine should not be given concomitantly with other cholinomimetic substances and might interfere with the activity of anticholinergic medicinal products.

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 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 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.

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

Adverse reactions in Table 1 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).

Table 1

Infections and infestations	
Very rare	Urinary infection
Metabolism and nutrition 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	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
Very common	Vomiting
Very common	Diarrhoea
Common	Abdominal pain and dyspepsia
Rare	Gastric 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

Table 2 shows the adverse reactions reported in patients with dementia associated with Parkison's disease treated with rivastigmine.

Table 2

Metabolism and nutrition disorders	
Common	Anorexia
Common	Dehydration
Psychiatric disorders	
Common	Insomnia
Common	Anxiety
Common	Restlessness
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
Uncommon	Dystonia
Cardiac disorders	
Common	Bradycardia
Uncommon	Atrial fibrillation
Uncommon	Atrioventricular block
Not known	Sick sinus syndrome
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
Musculoskeletal and connective tissue disorders	
Common	Muscle rigidity
General disorders and administration site conditions	
Common	Fatigue and asthenia
Common	Gait abnormality

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)
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 have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg 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 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.

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 (a performance based measure of cognition), the CIBIC-Plus (a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the PDS (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 ADAS-Cog 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	3.54[1]		n/a	

difference		
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	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 24 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 ADAS-Cog as a covariate. A positive change indicates improvement.
ITT: Intent-To-Treat; RDO: Retrieved Drop Outs

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.

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 ^{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.

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 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.

Subjects with 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.

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

Capsule contents
Microcrystalline cellulose
Hypromellose
Colloidal silicon dioxide

Magnesium stearate

Capsule shell
Titanium dioxide (E171)
Gelatin
Ink used for imprinting - Black S-1-17822/S-1-17823:
Shellac glaze-45%
Iron oxide black
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

- HDPE tablet container with a polypropylene cap and induction seal: 250 capsules
- 28, 56 or 112 capsules in transparent PVC/Alu push through blisters
- 50 x 1 capsules in PVC/Alu push through perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/001
EU/1/09/513/002
EU/1/09/513/003
EU/1/09/513/004
EU/1/09/513/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/04/2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 3 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 3 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Flesh colour cap imprinted with “R” & flesh color body imprinted with “3”

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 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 the 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 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 hepatic impairment have not been studied (see section 4.4)

Children
Rivastigmine is not recommended for use in children.

4.3 Contraindications

The use of this medicinal product is contraindicated in patients with

- hypersensitivity to the active substance, other carbamate derivatives or to any of the excipients used in the formulation,

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).

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.

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). Patients with severe hepatic impairment have not been studied. However, Rivastigmine Teva 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 recomemended 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 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 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 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.

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

Adverse reactions in Table 1 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).

Table 1 *

Infections and infestations	
Very rare	Urinary infection
Metabolism and nutrition 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	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
Very common	Vomiting
Very common	Diarrhoea
Common	Abdominal pain and dyspepsia
Rare	Gastric 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

Table 2 shows the adverse reactions reported in patients with dementia associated with Parkison's disease treated with rivastigmine.

Table 2

Metabolism and nutrition disorders	
Common	Anorexia
Common	Dehydration
Psychiatric disorders	
Common	Insomnia
Common	Anxiety
Common	Restlessness
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
Uncommon	Dystonia
Cardiac disorders	
Common	Bradycardia
Uncommon	Atrial fibrillation
Uncommon	Atrioventricular block
Not known	Sick sinus syndrome
Gastrointestinal disorders	
Very common	Nausea
Very common	Vomiting
Common	Diarrhoea
Common	Abdominal pain and dyspepsia
Common	Salivary hypersecretion
Hepatobililary disorders	
Not known	Heptatitis
Skin and subcutaneous tissue disorders	
Common	Hyperhydrosis
Musculoskeletal and connective tissue disorders	

Common	Muscle rigidity
General disorders and administration site conditions	
Common	Fatigue and asthenia
Common	Gait abnormality

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)
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 have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg 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 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.

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 (a performance based measure of cognition), the CIBIC-Plus (a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the PDS (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 ADAS-Cog 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	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 24 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 ADAS-Cog as a covariate. A positive change indicates improvement.
ITT: Intent-To-Treat; RDO: Retrieved Drop Outs

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.

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 ^{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.

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 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.

Subjects with 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.

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

Capsule contents
Microcrystalline cellulose
Hypromellose
Colloidal silicon dioxide
Magnesium stearate

Capsule shell
Red iron oxide (E 172)
Yellow iron oxide (E 172)
Titanium dioxide (E 171)
Gelatin

Ink used for imprinting - Black S-1-17822/S-1-17823
Shellac glaze-45%
Iron oxide black
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

- HDPE tablet container with a polypropylene cap and induction seal: 250 capsules
- 28, 56 or 112 capsules in transparent PVC/Alu push through blisters
- 50 x 1 capsules in PVC/Alu push through perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/006
EU/1/09/513/007
EU/1/09/513/008
EU/1/09/513/009
EU/1/09/513/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/04/2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 4.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 4.5 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Orange colour cap imprinted with “R” & orange color body imprinted with “4.5”.

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 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 the 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 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 hepatic impairment have not been studied (see section 4.4).

Children:
Rivastigmine is not recommended for use in children.

4.3 Contraindications

The use of this medicinal product is contraindicated in patients with

- hypersensitivity to the active substance, other carbamate derivatives or to any of the excipients used in the formulation,

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).

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.

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 the 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). Patients with severe hepatic impairment have not been studied. However, Rivastigmine Teva 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, rivastigmine should not be given concomitantly with other cholinomimetic substances and might interfere with the activity of anticholinergic medicinal products.

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 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 machinges. 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

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.

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

Adverse reactions in Table 1 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)

Table 1

Infections and infestations	
Very rare	Urinary infection
Metabolism and nutrition 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	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
Very common	Vomiting
Very common	Diarrhoea
Common	Abdominal pain and dyspepsia
Rare	Gastric 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).
Hepato-biliary 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

Table 2 shows the adverse reactions reported in patients with dementia associated with Parkinson's disease treated with rivastigmine.

Table 2

Metabolism and nutrition disorders	
Common	Anorexia
Common	Dehydration
Psychiatric disorders	
Common	Insomnia
Common	Anxiety
Common	Restlessness
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
Uncommon	Dystonia
Cardiac disorders	
Common	Bradycardia
Uncommon	Atrial fibrillation
Uncommon	Atrioventricular block
Not known	Sick sinus syndrome
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
Musculoskeletal and connective tissue disorders	
Common	Muscle rigidity
General disorders and administration site conditions	
Common	Fatigue and asthenia
Common	Gait abnormality

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)
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 have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may also occur. Ingestion of 46 mg 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 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.

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 (a performance based measure of cognition), the CIBIC-Plus (a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the PDS (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 ADAS-Cog 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	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 24 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 ADAS-Cog as a covariate. A positive change indicates improvement.
ITT: Intent-To-Treat; RDO: Retrieved Drop Outs

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.

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 ^{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.

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 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.

Subjects with 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.

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

Capsule contents
Microcrystalline cellulose
Hypromellose
Colloidal silicon dioxide
Magnesium stearate

Capsule shell
Red iron oxide (E172)
Yellow iron oxide (E 172)
Titanium dioxide (E171)
Gelatin
Ink used for imprinting - Black S-1-17822/S-1-17823
Shellac glaze-45%
Iron oxide black
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage instructions.

6.5 Nature and contents of container

- HDPE tablet container with a polypropylene cap and induction seal: 250 capsules
- 28, 56 or 112 capsules in transparent PVC/Alu push through blisters
- 50 x 1 capsules in PVC/Alu push through perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/011
EU/1/09/513/012
EU/1/09/513/013
EU/1/09/513/014
EU/1/09/513/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/04/2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 6 mg hard 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

Hard capsule

Orange cap imprinted with “R” & flesh color body imprinted with “6”

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 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 the 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 6mg 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 Parkison'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 hepatic impairment have not been studied (see section 4.4).

Children:
Rivastigmine is not recommended for use in children.

4.3 Contraindications

The use of this medicinal product is contraindicated in patients with

- hypersensitivity to the active substance, other carbamate derivatives or to any of the excipients used in the formulation.

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).

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.

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). Patients with severe hepatic impairment have not been studied. However, Rivastigmine Teva 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, rivastigmine should not be given concomitantly with other cholinomimetic substances and might interfere with the activity of anticholinergic medicinal products.

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 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 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.

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

Adverse reactions in Table 1 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).

Table 1

Infections and infestations	
Very rare	Urinary infection
Metabolism and nutrition 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	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
Very common	Vomiting
Very common	Diarrhoea
Common	Abdominal pain and dyspepsia
Rare	Gastric 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

Table 2 shows the adverse reactions reported in patients with dementia associated with Parkinson's disease treated with rivastigmine.

Table 2

Metabolism and nutrition disorders	
Common	Anorexia
Common	Dehydration
Psychiatric disorders	
Common	Insomnia
Common	Anxiety
Common	Restlessness
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
Uncommon	Dystonia
Cardiac disorders	
Common	Bradycardia
Uncommon	Atrial fibrillation
Uncommon	Atrioventricular block
Not known	Sick sinus syndrome
Gastrointestinal disorders	
Very common	Nausea
Very common	Vomiting
Common	Diarrhoea
Common	Abdominal pain and dyspesia
Common	Salivary hypersecretion
Hepatobiliary disorders	
Not known	Hepatitis
Skin and subcutaneous tissue disorders	
Common	Hyperhydrosis

Musculoskeletal and connective tissue disorders	
Common	Muscle rigidity
General disorders and administration site conditions	
Common	Fatigue and asthenia
Common	Gait abnormality

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)
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 have included nausea, vomiting and diarrhoea, hypertension or hallucinations. Due to the known vagotonic effect of cholinesterase inhibitors on heart rate, bradycardia and/or syncope may

also occur. Ingestion of 46 mg 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 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: N06D A03

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.

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 (a performance based measure of cognition), the CIBIC-Plus (a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the PDS (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 ADAS-Cog 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	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 24 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 ADAS-Cog as a covariate. A positive change indicates improvement.
ITT: Intent-To-Treat; RDO: Retrieved Drop Outs

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.

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 ^{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.

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 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.

Subjects with 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.

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

Capsule contents
Microcrystalline cellulose
Hypromellose
Colloidal silicon dioxide
Magnesium stearate

Capsule shell
Red iron oxide (E172)
Yellow iron oxide (E172)

Titanium dioxide (E171)
Gelatin
Ink used for imprinting - Black S-1-17822/S-1-17823
Shellac glaze-45%
Iron oxide black
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage instructions.

6.5 Nature and contents of container

- HDPE tablet container with a polypropylene cap and induction seal: 250 capsules
- 28, 56 or 112 capsules in transparent PVC/Alu push through blisters
- 50 x 1 capsules in PVC/Alu push through perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/016
EU/1/09/513/017
EU/1/09/513/018
EU/1/09/513/019
EU/1/09/513/020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/04/2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Teva Pharmaceutical Works Private Limited Company .
Pallagi út 13
4042 Debrecen
Hungary

TEVA Pharmaceutical Works Private Limited Company
H-2100 Gödöllő,
Táncsics Mihály út 82
Hungary

TEVA UK Ltd
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex,
BN22 9AG
United Kingdom

Pharmachemie B.V.
Swensweg 5,
2031 GA Haarlem
The Netherlands

TEVA Santé,
Rue Bellocier, 89100,
Sens,
France

Teva Czech Industries s.r.o.
Ostravska 29, c.p. 305
747 70 Opava-Komarov
Czech Republic

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, Section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

PSURs

The PSUR submission schedule for Rivastigmine TEVA hard capsules should follow PSURs submission schedule for the reference medicinal product.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – Rivastigmine Teva 1.5 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 1.5 mg hard capsules
Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 1.5 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Blisters
28 hard capsules
50 x 1 hard capsules
56 hard capsules
112 hard capsules

Bottles
250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
To be swallowed whole without crushing or opening
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/001
EU/1/09/513/002
EU/1/09/513/003
EU/1/09/513/004
EU/1/09/513/005

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivastigmine Teva 1.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister – Rivastigmine Teva 1.5 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 1.5 mg hard capsules
Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Tablet container - Self-adhesive, paper label – Rivastigmine Teva 1.5 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 1.5 mg hard capsules
Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 1.5 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
To be swallowed whole without crushing or opening.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/001
EU/1/09/513/002
EU/1/09/513/003
EU/1/09/513/004
EU/1/09/513/005

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – Rivastigmine Teva 3 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 3 mg hard capsules
Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 3 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Blisters
28 hard capsules
50 x 1 hard capsules
56 hard capsules
112 hard capsules

Bottles
250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
To be swallowed whole without crushing or opening
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/006
EU/1/09/513/007
EU/1/09/513/008
EU/1/09/513/009
EU/1/09/513/010

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivastigmine Teva 3 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister – Rivastigmine Teva 3 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 3 mg hard capsules
Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

Not applicable

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Tablet container - Self-adhesive, paper label – Rivastigmine Teva 3 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 3 mg hard capsules
Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 3 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
To be swallowed whole without crushing or opening.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/006
EU/1/09/513/007
EU/1/09/513/008
EU/1/09/513/009
EU/1/09/513/010

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – Rivastigmine Teva 4.5 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 4.5 mg hard capsules
Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 4.5 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Blisters
28 hard capsules
50 x 1 hard capsules
56 hard capsules
112 hard capsules

Bottles
250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
To be swallowed whole without crushing or opening
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/011
EU/1/09/513/012
EU/1/09/513/013
EU/1/09/513/014
EU/1/09/513/015

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivastigmine Teva 4.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister – Rivastigmine Teva 4.5 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 4.5 mg hard capsules
Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Tablet Container - Self-adhesive, paper label – Rivastigmine Teva 4.5 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 4.5 mg hard capsules
Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 4.5 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
To be swallowed whole without crushing or opening.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/011
EU/1/09/513/012
EU/1/09/513/013
EU/1/09/513/014
EU/1/09/513/015

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton – Rivastigmine Teva 6 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 6 mg hard capsules
Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 6 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Blisters
28 hard capsules
50 x 1 hard capsules
56 hard capsules
112 hard capsules

Bottles
250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
To be swallowed whole without crushing or opening
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Computerweg 10, 3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/016
EU/1/09/513/017
EU/1/09/513/018
EU/1/09/513/019
EU/1/09/513/020

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivastigmine Teva 6 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister – Rivastigmine Teva 6 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 6 mg hard capsules
Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Tablet container - Self-adhesive, paper label – Rivastigmine Teva 6 mg hard capsules

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine Teva 6 mg hard capsules
Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains rivastigmine hydrogen tartrate corresponding to rivastigmine 6 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
To be swallowed whole without crushing or opening.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10, 3542 DR Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/513/016
EU/1/09/513/017
EU/1/09/513/018
EU/1/09/513/019
EU/1/09/513/020

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Rivastigmine Teva 1.5 mg hard capsules
Rivastigmine Teva 3 mg hard capsules
Rivastigmine Teva 4.5 mg hard capsules
Rivastigmine Teva 6 mg hard capsules
Rivastigmine

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT RIVASTIGMINE TEVA IS AND WHAT IT IS USED FOR

The active substance of Rivastigmine Teva is rivastigmine

Rivastigmine belongs to a class of substances called cholinesterase inhibitors.

Rivastigmine Teva is used for the treatment of memory disorders in patients with Alzheimer's disease. It is also used for the treatment of dementia in patients with Parkinson's disease.

2. BEFORE YOU TAKE RIVASTIGMINE TEVA

Do NOT take Rivastigmine Teva

- If you are allergic (hypersensitive) to rivastigmine (the active substance in Rivastigmine Teva) or to any of the other ingredients of Rivastigmine Teva listed in section 6 of this leaflet
- If this applies to you, tell your doctor and do not take Rivastigmine Teva.

Take special care with Rivastigmine Teva

- if you have, or have ever had, irregular heartbeat.
- if you have, or have ever had, an active stomach ulcer.
- if you have, or have ever had, difficulties in passing urine.
- if you have, or have ever had, seizures.
- if you have, or have ever had, asthma or severe respiratory disease.
- if you have, or have ever had, impaired kidney function.
- if you have, or have ever had, impaired liver function.
- if you suffer from trembling.
- if you have a low body weight.

- If you have gastrointestinal reactions such as feeling sick (nausea) and being sick (vomiting) and diarrhoea. You may become dehydrated (losing too much fluid) if vomiting or diarhoea are prolonged.

If any of these apply to you, your doctor may need to monitor you more closely while you are on this medicine.

If you have not taken Rivastigmine Teva for several days, do not take the next dose until you have talked to your doctor.

The use of Rivastigmine Teva in children and adolescents (age below 18 years) is not recommended.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Rivastigmine Teva should not be given at the same time as other medicines with similar effects to Rivastigmine Teva. Rivastigmine Teva might interfere with anticholinergic medicines (medicines used to relieve stomach cramps or spasms, to treat Parkinson's disease or to prevent travel sickness).

If you have to undergo surgery whilst taking Rivastigmine Teva, tell your doctor before you are given any anaesthetics, because Rivastigmine Teva may exaggerate the effects of some muscle relaxants during anaesthesia.

Pregnancy and breast-feeding
Tell your doctor if you become pregnant during treatment. It is preferable to avoid the use of Rivastigmine Teva during pregnancy, unless clearly necessary.

You should not breast-feed during treatment with Rivastigmine Teva.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely.. Rivastigmine Teva may cause dizziness and somnolence, mainly at the start of treatment or when increasing the dose.If you feel dizzy or sleepy do not drive, use machines or perform any tasks that require your attention.

3. HOW TO TAKE RIVASTIGMINE TEVA

Always take Rivastigmine Teva exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

How to start treatment
Your doctor will tell you what dose of Rivastigmine Teva to take.
- Treatment usually starts with a low dose.
- Your doctor will slowly increase your dose depending on how you respond to the treatment.
- The highest dose that should be taken is 6.0 mg twice a day.

Your doctor will regularly check if the medicine is working for you. Your doctor will also monitor your weight whilst you are taking this medicine.

If you have not taken Rivastigmine Teva for several days, do not take the next dose until you have talked to your doctor.

Taking this medicine

- Tell your caregiver that you are taking Rivastigmine Teva.
- To benefit from your medicine, take it every day.
- Take Rivastigmine Teva twice a day, in the morning and evening, with food.
- Swallow the capsules whole with a drink.
- Do not open or crush the capsules.

If you take more Rivastigmine Teva than you should
If you accidentally take more Rivastigmine Teva than you should, inform your doctor. You may require medical attention. Some people who have accidentally taken too much Rivastigmine Teva have experienced feeling sick (nausea), being sick (vomiting), diarrhoea, high blood pressure and hallucinations. Slow heart beat and fainting may also occur.

If you forget to take Rivastigmine Teva
If you find you have forgotten to take your dose of Rivastigmine Teva, wait and take the next dose at the usual time. Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Rivastigmine Teva can cause side effects, although not everybody gets them.

You may have side effects more often when you start your medicine or when your dose is increased. Usually, the side effects slowly go away as your body gets used to the medicine.

The frequencies are defined as:
Very common (affects more than 1 patient in 10)
Common (affects 1 to 10 patients in 100)
Uncommon (affects 1 to 10 patients in 1,000)
Rare (affects 1 to 10 patients in 10, 000)
Very rare (affects less than 1 patient in 10,000)
Not known (frequency cannot be estimated from the available data)

Very common

- Feeling dizzy
- Loss of appetite
- Stomach problems such as feeling sick (nausea) or being sick (vomiting), diarrhoea

Common

- Anxiety
- Sweating
- Headache
- Heartburn
- Weight loss
- Stomach pain
- Feeling agitated
- Feeling tired or weak
- Generally feeling unwell
- Trembling or feeling confused

Uncommon

- Depression
- Difficulty in sleeping
- Fainting or accidentally falling
- Changes in how your liver is working

Rare
- Chest pain
- Rash, itching
  Fits (seizures)
- Ulcers in your stomach or intestine

Very rare
- High blood pressure
- Urinary tract infection
- Seeing things that are not there (hallucinations)
- Problems with your heartbeat such as fast or slow heartbeat
- Bleeding in the gut - shows as blood in stools or when being sick
- Inflammation of the pancreas – the signs include serious upper stomach pain, often with feeling sick (nausea) or being sick (vomiting)
- The signs of Parkinson's disease get worse or getting similar signs – such as stiff muscles, difficulty in carrying out movements

Not known
- Being violently sick (vomiting) that can cause tearing of the tube that connects your mouth with your stomach (oesophagus).
- Dehydration (losing too much fluid)
- Liver disorders (yellow skin, yellowing of the whites of eyes, abnormal darkening of the urine or unexplained nausea, vomiting, tiredness and loss of appetite)
- Aggression , feeling restless
- Uneven heartbeat

Patients with dementia and Parkinson's disease
These patients have some side effects more often. They also have some additional side effects:

Very common
- Trembling

Common
- Anxiety
- Feeling restless,
- Slow heartbeat
- Difficulty in sleeping
- Too much saliva and dehydration
- Unusually slow movements or movements you cannot control
- The signs of Parkinson's disease get worse or getting similar signs – such as stiff muscles, difficulty in carrying out movements

Uncommon
- Uneven heartbeat and poor control of movements

Other side effects seen with Rivastigmine transdermal patches and which may occur with hard capsules:

Common
- Fever
- Severe confusion

If you get any of these side effects, contact your doctor as you may need medical assistance.

If any of these side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE RIVASTIGMINE TEVA

Keep out of the reach and sight of children.

Do not use Rivastigmine Teva after the expiry date that is stated on the carton. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Rivastigmine Teva contains

The active substance is rivastigmine
Rivastigmine Teva 1.5 mg hard capsules contains 1.5 mg rivastigmine as rivastigmine hydrogen tartrate
Rivastigmine Teva 3 mg hard capsules contains 3 mg rivastigmine as rivastigmine hydrogen tartrate
Rivastigmine Teva 4.5 mg hard capsules contains 4.5 mg rivastigmine as rivastigmine hydrogen tartrate
Rivastigmine Teva 6 mg hard capsules contains 6 mg rivastigmine as rivastigmine hydrogen tartrate

The other ingredients are:
Capsule contents - microcrystalline cellulose, hypromellose, colloidal silicon dioxide, magnesium stearate.
Capsule shell – titanium dioxide (E171), gelatin and ink used for imprinting Black S-1-17822/S-1-17823 (shellac glaze-45% in ethanol containing iron oxide black, N-butyl alcohol, isopropyl alcohol, propylene alcohol and ammonium hydroxide). In addition, Rivastigmine Teva 3 mg, 4.5 mg and 6 mg hard capsules contain red iron oxide (E172) and yellow iron oxide (E 172).

What Rivastigmine Teva looks like and contents of the pack

Hard capsule

- Rivastigmine Teva 1.5 mg hard capsules: White cap imprinted with “R” & white body imprinted with “1.5”
- Rivastigmine Teva 3 mg hard capsules: Flesh colour cap imprinted with “R” & flesh colour body imprinted with “3”
- Rivastigmine Teva 4.5 mg hard capsules: Orange colour cap imprinted with “R” & orange colour body imprinted with “4.5”
- Rivastigmine Teva 6 mg hard capsules: Orange cap imprinted with “R” & flesh colour body imprinted with “6”

Rivastigmine Teva hard capsules are available in blister packs of 28, 56 and 112 capsules, perforated blisters containing 50 x 1 capsules, and bottles containing 250 capsules.

Marketing Authorisation Holder

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This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu