ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains rivastigmine hydrogen tartrate corresponding to 1.5 mg rivastigmine.
Each capsule contains rivastigmine hydrogen tartrate corresponding to 3 mg rivastigmine.
Each capsule contains rivastigmine hydrogen tartrate corresponding to 4.5 mg rivastigmine.
Each capsule contains rivastigmine hydrogen tartrate corresponding to 6 mg rivastigmine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Off-white to slightly yellow powder in a capsule with yellow cap and yellow body, with red imprint "RIV 1.5 mg" on the body.

Off-white to slightly yellow powder in a capsule with orange cap and orange body, with red imprint "RIV 3 mg" on the body.

Off-white to slightly yellow powder in a capsule with red cap and red body, with white imprint "RIV 4.5 mg" on the body.

Off-white to slightly yellow powder in a capsule with red cap and orange body, with red imprint "RIV 6 mg" on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

Initial dose
1.5 mg twice a day.

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

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

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

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

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

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

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

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

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

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

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

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

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

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

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

Dose titration: Adverse reactions (e.g. hypertension and hallucinations in patients with Alzheimer's dementia and worsening of extrapyramidal symptoms, in particular tremor, in patients with dementia associated with Parkinson's disease) have been observed shortly after dose increase. They may respond to a dose reduction. In other cases, rivastigmine has been discontinued (see section 4.8).

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

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

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

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).

Electrocardiogram QT prolongation may occur in patients treated with certain cholinesterase inhibitor products including rivastigmine. Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients with pre-existing, or a family history of, QTc prolongation or at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with

medicinal products known to induce QT prolongation and/or torsade de pointes**.** Clinical monitoring (ECG) may also be required (see sections 4.5 and 4.8).

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

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

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

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

Table 1

Infections and infestations	
Very rare	Urinary infection
Metabolism and nutrition disorders	
Very common	Anorexia
Common	Decreased appetite
Not known	Dehydration
Psychiatric disorders	
Common	Agitation
Common	Confusion
Common	Anxiety
Common	Nightmares
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)
Not known	Pleurothotonus (Pisa syndrome)
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, allergic dermatitis (disseminated)
General disorders and administration site conditions	
Common	Fatigue and asthenia
Common	Malaise
Uncommon	Fall
Investigations	
Common	Weight loss

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

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

Table 2

Metabolism and nutrition disorders	
Common	Decreased appetite
Common	Dehydration
Psychiatric disorders	
Common	Insomnia
Common	Anxiety
Common	Restlessness
Common	Hallucination, visual
Common	Depression
Not known	Aggression
Nervous system disorders	
Very common	Tremor
Common	Dizziness
Common	Somnolence
Common	Headache
Common	Parkinson's disease (worsening)
Common	Bradykinesia
Common	Dyskinesia
Common	Hypokinesia
Common	Cogwheel rigidity
Uncommon	Dystonia
Not known	Pleurothotonus (Pisa syndrome)
Cardiac disorders	
Common	Bradycardia
Uncommon	Arial fibrillation
Uncommon	Atrioventricular block
Not known	Sick sinus syndrome
Vascular disorders	
Common	Hypertension
Uncommon	Hypotension

Gastrointestinal disorders	
Very common	Nausea
Very common	Vomiting
Common	Diarrhoea
Common	Abdominal pain and dyspepsia
Common	Salivary hypersecretion
Hepatobiliary disorders	
Not known	Hepatitis
Skin and subcutaneous tissue disorders	
Common	Hyperhydrosis
Not known	Allergic dermatitis (disseminated)
General disorders and administration site conditions	
Very common	Fall
Common	Fatigue and asthenia
Common	Gait disturbance
Common	Parkinson gait

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

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

Table 3

Pre-defined adverse events that may reflect worsening of parkinsonian symptoms in patients with dementia associated with Parkinson's disease	**Rivastigmine n (%)**	**Placebo n (%)**
Total patients studied	362 (100)	179 (100)
Total patients with pre-defined AE(s)	99 (27.3)	28 (15.6)
Tremor	37 (10.2)	7 (3.9)
Fall	21 (5.8)	11 (6.1)
Parkinson's disease (worsening)	12 (3.3)	2 (1.1)
Salivary hypersecretion	5 (1.4)	0
Dyskinesia	5 (1.4)	1 (0.6)
Parkinsonism	8 (2.2)	1 (0.6)
Hypokinesia	1 (0.3)	0
Movement disorder	1 (0.3)	0
Bradykinesia	9 (2.5)	3 (1.7)
Dystonia	3 (0.8)	1 (0.6)
Gait abnormality	5 (1.4)	0
Muscle rigidity	1 (0.3)	0
Balance disorder	3 (0.8)	2 (1.1)
Musculoskeletal stiffness	3 (0.8)	0
Rigors	1 (0.3)	0
Motor dysfunction	1 (0.3)	0

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

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

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, 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 (Alzheimer's Disease Assessment Scale – Cognitive subscale, a performance based measure of cognition), the CIBIC-Plus (Clinician's Interview Based Impression of Change-Plus, a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the PDS (Progressive Deterioration Scale, a caregiver-rated assessment of the activities of daily living including personal hygiene, feeding, dressing, household chores such as

shopping, retention of ability to orient oneself to surroundings as well as involvement in activities relating to finances, etc.).

The 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

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

5.2 Pharmacokinetic properties

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

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

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

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

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

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

Elderly population
While bioavailability of rivastigmine is greater in elderly than in young healthy volunteers, studies in Alzheimer patients aged between 50 and 92 years showed no change in bioavailability with age.

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

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

5.3 Preclinical safety data

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rivastigmine HEXAL 1.5 mg hard capsules:

Capsule shell:
- Gelatin
- Titanium dioxide (E171)
- Yellow iron oxide (E172)

Capsule fill:
- Microcrystaline cellulose
- Magnesium stearate
- Hypromellose
- Silica, colloidal anhydrous

Printing ink:
- Shellac
- Red iron oxide (E172)

Rivastigmine HEXAL 3 mg and 6 mg hard capsules:

Capsule shell:
- Gelatin
- Titanium dioxide (E171)
- Yellow iron oxide (E172)
- Red iron oxide (E172)

Capsule fill:
- Microcrystaline cellulose
- Magnesium stearate
- Hypromellose
- Silica, colloidal anhydrous

Printing ink:
- Shellac
- Red iron oxide (E172)

Rivastigmine HEXAL 4.5 mg hard capsules:

Capsule shell:
- Gelatin
- Titanium dioxide (E171)
- Yellow iron oxide (E172)
- Red iron oxide (E172)

Capsule fill:
- Microcrystaline cellulose
- Magnesium stearate
- Hypromellose
- Silica, colloidal anhydrous

Printing ink:
- Shellac
- Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

- Blister of clear PVC tray with blue lidding foil with 14 capsules. Each box contains 28, 56 or 112 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

HEXAL AG
Industriestraße 25
83607 Holzkirchen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

Rivastigmine HEXAL 1.5 mg hard capsules:

EU/1/09/589/001
EU/1/09/589/002
EU/1/09/589/003
EU/1/09/589/004

Rivastigmine HEXAL 3 mg hard capsules:

EU/1/09/589/005
EU/1/09/589/006
EU/1/09/589/007
EU/1/09/589/008

Rivastigmine HEXAL 4.5 mg hard capsules:

EU/1/09/589/009
EU/1/09/589/010
EU/1/09/589/011
EU/1/09/589/012

Rivastigmine HEXAL 6 mg hard capsules:

EU/1/09/589/013
EU/1/09/589/014
EU/1/09/589/015
EU/1/09/589/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 11/12/2009
Date of first renewal: 11/07/2014

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine HEXAL 2 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains rivastigmine hydrogen tartrate corresponding to 2 mg rivastigmine.

Excipient with known effect
Each ml contains 1 mg of sodium benzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Clear, yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

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

Initial dose
1.5 mg twice a day.

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

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

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

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

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

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

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

Renal and hepatic impairment
No dose adjustment is necessary for patients with mild to moderate renal or hepatic impairment.

However, due to increased exposure in these populations, dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant renal or hepatic impairment might experience more dose-dependent adverse reactions.

Patients with severe hepatic impairment have not been studied, however, rivastigmine oral solution may be used in this patient population provided close monitoring is exercised (see sections 4.4 and 5.2).

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

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

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

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

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

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

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

Patients and caregivers should be instructed accordingly.

Dose titration: Adverse reactions (e.g. hypertension and hallucinations in patients with Alzheimer's dementia and worsening of extrapyramidal symptoms, in particular tremor, in patients with dementia associated with Parkinson's disease) have been observed shortly after dose increase. They may respond to a dose reduction. In other cases, rivastigmine has been discontinued (see section 4.8).

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

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

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

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).

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

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.

One of the excipients in Rivastigmine HEXAL oral solution is sodium benzoate. Benzoic acid is a mild irritant to the skin, eyes and mucous membrane.

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

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

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

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

Rivastigmine HEXAL contains benzoate salt and sodium
This medicinal product contains 1 mg sodium benzoate in each ml of oral solution.
This medicinal product contains less than 1 mmol (23 mg) sodium in each ml of oral solution, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

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

Table 1

Infections and infestations	
Very rare	Urinary infection
Metabolism and nutrition disorders	
Very common	Anorexia
Common	Decreased appetite
Not known	Dehydration
Psychiatric disorders	
Common	Agitation
Common	Confusion
Common	Anxiety
Common	Nightmares
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)
Not known	Pleurothotonus (Pisa syndrome)
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, allergic dermatitis (disseminated)
General disorders and administration site conditions	
Common	Fatigue and asthenia
Common	Malaise

Uncommon	Fall
Investigations	
Common	Weight loss

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

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

Table 2

Metabolism and nutrition disorders	
Common	Decreased appetite
Common	Dehydration
Psychiatric disorders	
Common	Insomnia
Common	Anxiety
Common	Restlessness
Common	Hallucination, visual
Common	Depression
Not known	Aggression
Nervous system disorders	
Very common	Tremor
Common	Dizziness
Common	Somnolence
Common	Headache
Common	Parkinson's disease (worsening)
Common	Bradykinesia
Common	Dyskinesia
Common	Hypokinesia
Common	Cogwheel rigidity
Uncommon	Dystonia
Not known	Pleurothotonus (Pisa syndrome)
Cardiac disorders	
Common	Bradycardia
Uncommon	Arial fibrillation
Uncommon	Atrioventricular block
Not known	Sick sinus syndrome
Vascular disorders	
Common	Hypertension
Uncommon	Hypotension
Gastrointestinal disorders	
Very common	Nausea
Very common	Vomiting
Common	Diarrhoea
Common	Abdominal pain and dyspepsia
Common	Salivary hypersecretion
Hepatobiliary disorders	
Not known	Hepatitis
Skin and subcutaneous tissue disorders	
Common	Hyperhydrosis
Not known	Allergic dermatitis (disseminated)

General disorders and administration site conditions	
Very common	Fall
Common	Fatigue and asthenia
Common	Gait disturbance
Common	Parkinson gait

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

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

Table 3

Pre-defined adverse events that may reflect worsening of parkinsonian symptoms in patients with dementia associated with Parkinson's disease	**Rivastigmine n (%)**	**Placebo n (%)**
Total patients studied	362 (100)	179 (100)
Total patients with pre-defined AE(s)	99 (27.3)	28 (15.6)
Tremor	37 (10.2)	7 (3.9)
Fall	21 (5.8)	11 (6.1)
Parkinson's disease (worsening)	12 (3.3)	2 (1.1)
Salivary hypersecretion	5 (1.4)	0
Dyskinesia	5 (1.4)	1 (0.6)
Parkinsonism	8 (2.2)	1 (0.6)
Hypokinesia	1 (0.3)	0
Movement disorder	1 (0.3)	0
Bradykinesia	9 (2.5)	3 (1.7)
Dystonia	3 (0.8)	1 (0.6)
Gait abnormality	5 (1.4)	0
Muscle rigidity	1 (0.3)	0
Balance disorder	3 (0.8)	2 (1.1)
Musculoskeletal stiffness	3 (0.8)	0
Rigors	1 (0.3)	0
Motor dysfunction	1 (0.3)	0

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product, Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

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

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, 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 (Alzheimer's Disease Assessment Scale - Cognitive subscale, a performance based measure of cognition), the CIBIC-Plus (Clinician's Interview Based Impression of Change-Plus, a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the PDS (Progressive Deterioration Scale, a caregiver-rated assessment of the activities of daily living including personal hygiene, feeding, dressing, household chores such as shopping, retention of ability to orient oneself to surroundings as well as involvement in activities relating to finances, etc.).

The 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

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

5.2 Pharmacokinetic properties

Absorption
Rivastigmine is rapidly and completely absorbed. Peak plasma concentrations are reached in approximately 1 hour. As a consequence of rivastigmine's interaction with its target enzyme, the increase in bioavailability is about 1.5-fold greater than that expected from the increase in dose. Absolute bioavailability after a 3 mg dose is about 36%±13%. Administration of rivastigmine oral solution with food delays absorption (t_{max}) by 74 min and lowers C_{max} by 43% and increases AUC by approximately 9%.

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

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

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

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

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

Elderly population
While bioavailability of rivastigmine is greater in elderly than in young healthy volunteers, studies in Alzheimer patients aged between 50 and 92 years showed no change in bioavailability with age.

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

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

5.3 Preclinical safety data

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E 211)
Citric acid
Sodium citrate
Quinoline yellow WS dye (E104)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
Rivastigmine HEXAL oral solution should be used within 1 month of opening the bottle.

6.4 Special precautions for storage

Do not store above 30°C. Do not refrigerate or freeze.

Store in an upright position.

6.5 Nature and contents of container

Type III amber glass bottle with a child-resistant cap, dip tube and self aligning plug. 50 ml or 120 ml bottle. The oral solution is packaged with an oral dosing syringe in a plastic tube container.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

HEXAL AG
Industriestraße 25
83607 Holzkirchen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/589/017
EU/1/09/589/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/12/2009
Date of first renewal: 11/07/2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARDS TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Hard gelatine capsules
Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Roonstrasse 25
90429 Nürnberg
Germany

Salutas Pharma Gmbh
Otto-Von-Guericke-Allee 1, Barleben,
Saxony-Anhalt, 39179,
Germany

Oral solution
Novartis Pharma GmbH
Roonstrasse 25
D-90429 Nuremberg
Germany

Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes 764,
08013 Barcelona
Spain

Salutas Pharma Gmbh
Otto-Von-Guericke-Allee 1, Barleben,
Saxony-Anhalt, 39179,
Germany

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 OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARDS TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and intervention detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR ALU/PVC BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine HEXAL 1.5 mg hard capsules

rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 1.5 mg of rivastigmine (as hydrogen tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

HEXAL AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/589/001
EU/1/09/589/002
EU/1/09/589/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivastigmine HEXAL 1.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ALU/PVC BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine HEXAL 1.5 mg hard capsules

rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

HEXAL AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ALU/PVC BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine HEXAL 3 mg hard capsules

rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

HEXAL AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR ALU/PVC BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine HEXAL 4.5 mg hard capsules

rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4.5 mg of rivastigmine (as hydrogen tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

HEXAL AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/589/009
EU/1/09/589/010
EU/1/09/589/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivastigmine HEXAL 4.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ALU/PVC BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine HEXAL 4.5 mg hard capsules

rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

HEXAL AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunda

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR ALU/PVC BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine HEXAL 6 mg hard capsules

rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 6 mg of rivastigmine (as hydrogen tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

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

HEXAL AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/589/013
EU/1/09/589/014
EU/1/09/589/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rivastigmine HEXAL 6 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ALU/PVC BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine HEXAL 6 mg hard capsules

rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

HEXAL AG

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON FOR GLASS BOTTLE
LABEL FOR GLASS BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

Rivastigmine HEXAL 2 mg/ml oral solution

rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 2.0 mg of rivastigmine (as hydrogen tartrate).

3. LIST OF EXCIPIENTS

Contains sodium benzoate (E 211). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

50 ml oral solution
120 ml oral solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

After opening: 1 month

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Do not refrigerate or freeze.
Store in an upright position.

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

HEXAL AG
Industriestraße 25
83607 Holzkirchen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/09/589/017
EU/1/09/589/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Only for carton box:
Rivastigmine HEXAL 2 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

Only for carton box:

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Only for carton box:

PC
SN

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rivastigmine HEXAL 1.5 mg hard capsules
Rivastigmine HEXAL 3 mg hard capsules
Rivastigmine HEXAL 4.5 mg hard capsules
Rivastigmine HEXAL 6 mg hard capsules
rivastigmine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only . Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects , talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rivastigmine HEXAL is and what it is used for

The active substance of Rivastigmine HEXAL is rivastigmine.

Rivastigmine belongs to a class of substances called cholinesterase inhibitors.

In patients with Alzheimer's dementia or dementia due to Parkinson's disease, certain nerve cells die in the brain, resulting in low levels of the neurotransmitter acetylcholine (a substance that allows nerve cells to communicate with each other). Rivastigmine works by blocking the enzymes that break down acetylcholine: acetylcholinesterase and butyrylcholinesterase. By blocking these enzymes, Rivastigmine allows levels of acetylcholine to be increased in the brain, helping to reduce the symptoms of Alzheimer's disease and dementia associated with Parkinson's disease.

Rivastigmine HEXAL is used for the treatment of adult patients with mild to moderately severe Alzheimer's dementia, a progressive brain disorder that gradually affects memory, intellectual ability and behaviour. The capsules and oral solution can also be used for the treatment of dementia in adult patients with Parkinson's disease.

2. What you need to know before you take Rivastigmine HEXAL

Do not take Rivastigmine HEXAL
- if you are allergic to rivastigmine (the active substance in Rivastigmine HEXAL) or any of the other ingredients of this medicine (listed in section 6).
- if you have had a previous skin reaction suggestive of allergic contact dermatitis with rivastigmine.

If this applies to you, tell your doctor and do not take Rivastigmine HEXAL.

Warnings and precautions
Talk to your doctor before taking Rivastigmine HEXAL
- if you have, or have ever had, a heart condition such as an irregular or slow heartbeat, QTc prolongation, a family history of QTc prolongation, torsade de pointes, or have a low blood level of potassium or magnesium.
- 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), being sick (vomiting) and diarrhoea. You may become dehydrated (losing too much fluid) if vomiting or diarrhoea 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 HEXAL for more than three days, do not take the next dose until you have talked to your doctor.

Children and adolescents
There is no relevant use of Rivastigmine HEXAL in the paediatric population in the treatment of Alzheimer's disease.

Other medicines and Rivastigmine HEXAL
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

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

Rivastigmine Hexal should not be given at the same time as metoclopramide (a medicine used to relieve or prevent nausea and vomiting). Taking the two medicines together could cause problems such as stiff limbs and trembling hands.

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

Caution when Rivastigmine HEXAL is taken together with beta-blockers (medicines such as atenolol used to treat hypertension, angina and other heart conditions). Taking the two medicines together could cause problems such as slowing of the heartbeat (bradycardia) leading to fainting or loss of consciousness.

Caution when Rivastigmine HEXAL is taken together with other medicines that can affect your heart rhythm or the electrical system of your heart (QT prolongation).

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are pregnant, the benefits of using Rivastigmine HEXAL must be assessed against the possible effects on your unborn child. Rivastigmine HEXAL should not be used during pregnancy unless clearly necessary.

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

Driving and using machines
Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely. Rivastigmine HEXAL 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 HEXAL

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How to start treatment
Your doctor will tell you what dose of Rivastigmine HEXAL to take.
- Treatment usually starts with a low dose.
- Your doctor will slowly increase your dose depending on how you respond to 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 HEXAL for more than three 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 HEXAL.
- To benefit from your medicine, take it every day.
- Take Rivastigmine HEXAL 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 HEXAL than you should
If you accidentally take more Rivastigmine HEXAL than you should, inform your doctor. You may require medical attention. Some people who have accidentally taken too much Rivastigmine HEXAL have experienced feeling sick (nausea), being sick (vomiting), diarrhoea, high blood pressure and hallucinations. Slow heartbeat and fainting may also occur.

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

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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 will slowly go away as your body gets used to the medicine.

Very common (may affect more than 1 in 10 people)
- Feeling dizzy
- Loss of appetite
- Stomach problems such as feeling sick (nausea) or being sick (vomiting), diarrhoea

Common (may affect up to 1 in 10 people)
- Anxiety
- Sweating
- Headache
- Heartburn
- Weight loss
- Stomach pain
- Feeling agitated
- Feeling tired or weak
- Generally feeling unwell
- Trembling or feeling confused
- Decreased appetite
- Nightmares

Uncommon (may affect up to 1 in 100 people)
- Depression
- Difficulty in sleeping
- Fainting or accidentally falling
- Changes in how well your liver is working

Rare (may affect up to 1 in 1,000 people)
- Chest pain
- Rash, itching
- Fits (seizures)
- Ulcers in your stomach or intestine

Very rare (may affect up to 1 in 10,000 people)
- 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 (frequency cannot be estimated from the available data)
- 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 the eyes, abnormal darkening of the urine or unexplained nausea, vomiting, tiredness and loss of appetite)
- Aggression, feeling restless
- Uneven heartbeat
- Pisa syndrome (a condition involving involuntary muscle contraction with abnormal bending of the body and head to one side)

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

Very common (may affect more than 1 in 10 people)

- Trembling
- Fainting
- Accidentally falling

Common (may affect up to 1 in 10 people)
- Anxiety
- Feeling restless
- Slow and fast 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 and muscle weakness

Uncommon (may affect up to 1 in 100 people)
- Uneven heartbeat and poor control of movements

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

Common (may affect up to 1 in 10 people)
- Fever
- Severe confusion
- Urinary incontinence (inability to retain adequate urine)

Uncommon (may affect up to 1 in 100 people)
- Hyperactivity (high level of activity, restlessness)

Not known (frequency cannot be estimated from the available data)
- Allergic reaction where the patch was used, such as blisters or skin inflammation

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

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Rivastigmine Hexal

Keep this medicine out of the sight and reach of children.

Do not use Rivastigmine HEXAL after the expiry date which is stated on the blister, bottle label and carton after "EXP". The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Rivastigmine HEXAL contains
- The active substance is rivastigmine.
- The other ingredients are: hypromellose, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica, gelatin, yellow iron oxide red iron oxide, titanium dioxide, and shellac.

Each Rivastigmine HEXAL 1.5 mg capsule contains 1.5 mg of rivastigmine.
Each Rivastigmine HEXAL 3 mg capsule contains 3 mg of rivastigmine.
Each Rivastigmine HEXAL 4.5 mg capsule contains 4.5 mg of rivastigmine.
Each Rivastigmine HEXAL 6 mg capsule contains 6 mg of rivastigmine.

What Rivastigmine HEXAL looks like and contents of the pack
- Rivastigmine HEXAL 1.5 mg hard capsules, which contain an off-white to slightly yellow powder, have a yellow cap and yellow body, with a red imprint “RIV 1.5 mg” on the body.

- Rivastigmine HEXAL 3 mg hard capsules, which contain an off-white to slightly yellow powder, have an orange cap and orange body, with a red imprint “RIV 3 mg” on the body.

- Rivastigmine HEXAL 4.5 mg hard capsules, which contain an off-white to slightly yellow powder, have a red cap and red body, with a white imprint “RIV 4.5 mg” on the body.

- Rivastigmine HEXAL 6 mg hard capsules, which contain an off-white to slightly yellow powder, have a red cap and orange body, with a red imprint “RIV 6 mg” on the body.

They are packed in blisters available in three different pack sizes (28, 56 or 112 capsules) but these may not all be available in your country.

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This leaflet was last revised in
Detailed information on this medicine is available on the European Medicines Agency (EMA) website: http://www.ema.europa.eu/

Package leaflet: Information for the patient

Rivastigmine HEXAL 2 mg/ml oral solution
rivastigmine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects , talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet

1. What Rivastigmine HEXAL is and what it is used for

The active substance of Rivastigmine HEXAL is rivastigmine.

Rivastigmine belongs to a class of substances called cholinesterase inhibitors.

In patients with Alzheimer's dementia or dementia due to Parkinson's disease, certain nerve cells die in the brain, resulting in low levels of the neurotransmitter acetylcholine (a substance that allows nerve cells to communicate with each other). Rivastigmine works by blocking the enzymes that break down acetylcholine: acetylcholinesterase and butyrylcholinesterase. By blocking these enzymes, Rivastigmine HEXAL allows levels of acetylcholine to be increased in the brain, helping to reduce the symptoms of Alzheimer's disease and dementia associated with Parkinson's disease.

Rivastigmine HEXAL is used for the treatment of adult patients with mild to moderately severe Alzheimer's dementia, a progressive brain disorder that gradually affects memory, intellectual ability and behaviour. The capsules and oral solution can also be used for the treatment of dementia in adult patients with Parkinson's disease.

2. What you need to know before you take Rivastigmine HEXAL

Do not take Rivastigmine HEXAL
- if you are allergic to rivastigmine (the active substance in Rivastigmine HEXAL) or any of the other ingredients of this medicine (listed in section 6).
- if you have had a previous skin reaction suggestive of allergic contact dermatitis with rivastigmine.

If this applies to you, tell your doctor and do not take Rivastigmine HEXAL.

Warnings and precautions
Talk to your doctor before taking Rivastigmine HEXAL
- if you have, or have ever had, a heart condition such as an irregular or slow heartbeat, QTc prolongation, a family history of QTc prolongation, torsade de pointes, or have a low blood level of potassium or magnesium.
- 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), being sick (vomiting) and diarrhoea. You may become dehydrated (losing too much fluid) if vomiting or diarrhoea 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 HEXAL for more than three days, do not take the next dose until you have talked to your doctor.

Children and adolescents
There is no relevant use of Rivastigmine HEXAL in the paediatric population in the treatment of Alzheimer's disease.

Other medicines and Rivastigmine HEXAL
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

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

Rivastigmine HEXAL should not be given at the same time as metoclopramide (a medicine used to relieve or prevent nausea and vomiting). Taking the two medicines together could cause problems such as stiff limbs and trembling hands.

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

Caution when Rivastigmine HEXAL is taken together with beta-blockers (medicines such as atenolol used to treat hypertension, angina and other heart conditions). Taking the two medicines together could cause problems such as slowing of the heartbeat (bradycardia) leading to fainting or loss of consciousness.

Caution when Rivastigmine HEXAL is taken together with other medicines that can affect your heart rhythm or the electrical system of your heart (QT prolongation).

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

If you are pregnant, the benefits of using Rivastigmine HEXAL must be assessed against the possible effects on your unborn child. Rivastigmine HEXAL should not be used during pregnancy unless clearly necessary

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

Driving and using machines
Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely. Rivastigmine HEXAL 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.

Rivastigmine HEXAL contains benzoate salt and sodium
This medicine contains 1 mg sodium benzoate in each ml of oral solution.
This medicine contains less than 1 mmol (23 mg) sodium in each ml of oral solution, that is to say essentially 'sodium-free'.

3. How to take Rivastigmine HEXAL

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

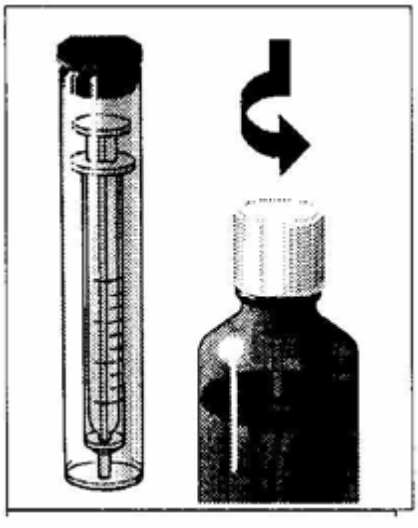
How to start treatment
Your doctor will tell you what dose of Rivastigmine HEXAL to take.
- Treatment usually starts with a low dose.
- Your doctor will slowly increase your dose depending on how you respond to the treatment.
- The highest dose that should be taken is 6.0 mg (corresponding to 3 ml) twice 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 HEXAL for more than three days, do not take the next dose until you have talked to your doctor.

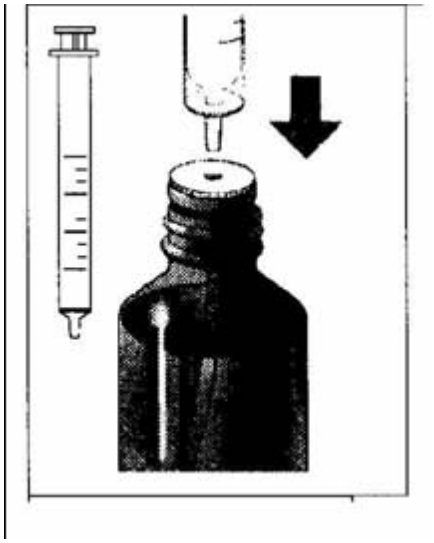
Taking this medicine
- Tell your caregiver that you are taking Rivastigmine HEXAL.
- To benefit from your medicine, take it every day.
- Take Rivastigmine HEXAL twice a day, in the morning and evening, with food.

How to use this medicine



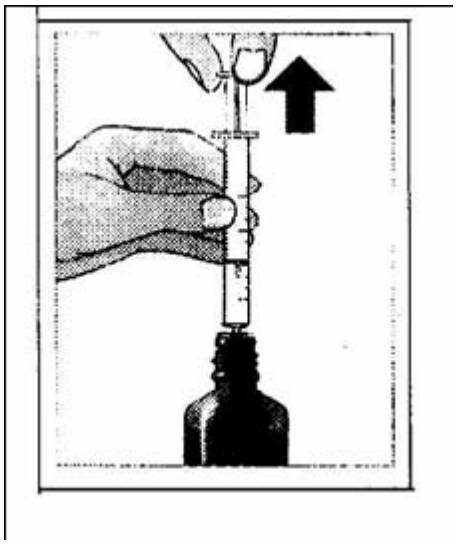
1. Preparing the bottle and syringe

- Take the syringe out of its protective case.
- Push down and turn the child resistant cap to open bottle.



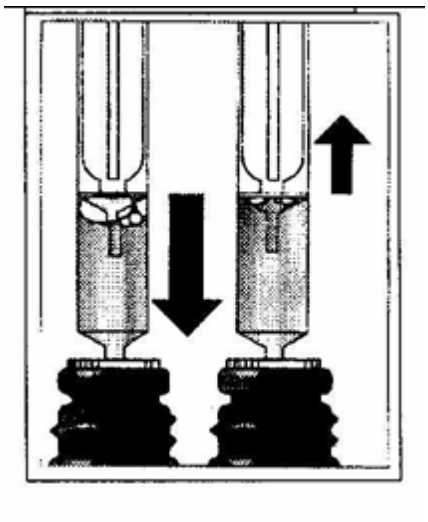
2. Attaching the syringe to the bottle

- Push the nozzle of the syringe into the hole in the white stopper.



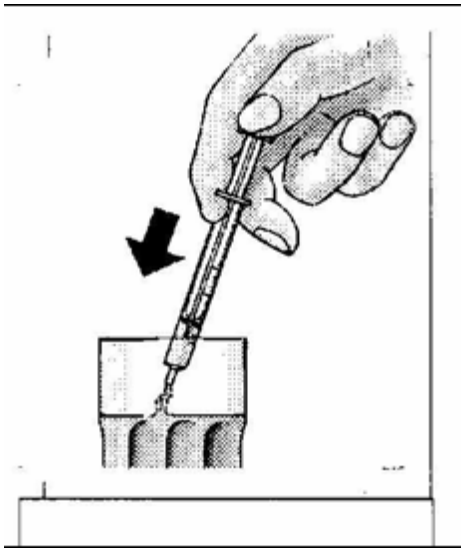
3. Filling the syringe

- Pull the plunger upwards until it reaches the right mark for the dose that your doctor has prescribed.



4. Removing bubbles

- Push down and pull up the plunger a few times to get rid of any large bubbles.
- A few tiny bubbles are not important and will not affect your dose in any way.
- Check the dose is still correct.
- Then, remove the syringe from the bottle.



5. Taking your medicine

- Swallow your medicine straight from the syringe.
- You can also mix your medicine with water in a small glass. Stir and drink all of the mixture.

6. After using the syringe
- Wipe the outside of the syringe with a clean tissue.
- Then, put the syringe back in its protective case.
- Put the child resistant cap back on the bottle to close it.

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

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

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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 will slowly go away as your body gets used to the medicine.

Very common (may affect more than 1 in 10 people)
- Feeling dizzy
- Loss of appetite
- Stomach problems such as feeling sick (nausea) or being sick (vomiting), diarrhoea

Common (may affect up to 1 in 10 people)
- Anxiety
- Sweating
- Headache
- Heartburn
- Weight loss
- Stomach pain
- Feeling agitated
- Feeling tired or weak
- Generally feeling unwell
- Trembling or feeling confused
- Decreased appetite
- Nightmares

Uncommon (may affect up to 1 in 100 people)
- Depression
- Difficulty in sleeping
- Fainting or accidentally falling
- Changes in how well your liver is working

Rare (may affect up to 1 in 1,000 people)
- Chest pain
- Rash, itching
- Fits (seizures)
- Ulcers in your stomach or intestine

Very rare (may affect up to 1 in 10,000 people)
- 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 (frequency cannot be estimated from the available data)
- 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 the eyes, abnormal darkening of the urine or unexplained nausea, vomiting, tiredness and loss of appetite)
- Aggression, feeling restless
- Uneven heartbeat
- Pisa syndrome (a condition involving involuntary muscle contraction with abnormal bending of the body and head to one side)

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

Very common (may affect more than 1 in 10 people)
- Trembling
- Fainting
- Accidentally falling

Common (may affect up to 1 in 10 people)
- Anxiety
- Feeling restless
- Slow and fast 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 and muscle weakness

Uncommon (may affect up to 1 in 100 people)
- Uneven heartbeat and poor control of movements

Other side effects seen with transdermal patches and which may occur with the oral solution:

Common (may affect up to 1 in 10 people)
- Fever
- Severe confusion
- Urinary incontinence (inability to retain adequate urine)

Uncommon (may affect up to 1 in 100 people)
- Hyperactivity (high level of activity, restlessness)

Not known (frequency cannot be estimated from the available data)
- Allergic reaction where the patch was used, such as blisters or skin inflammation

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

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE RIVASTIGMINE HEXAL

Keep this medicine out of the sight and reach of children.

Do not use Rivastigmine HEXAL after the expiry date which is stated on the bottle label and carton after "EXP". The expiry date refers to the last day of that month.

Do not store above 30°C. Do not refrigerate or freeze.

Store in an upright position.

Use Rivastigmine HEXAL oral solution within 1 month of opening the bottle.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Content of the pack and other information

What Rivastigmine HEXAL contains
- The active substance is rivastigmine. Each ml contains rivastigmine hydrogen tartrate corresponding to rivastigmine base 2.0 mg.
- The other ingredients are: sodium benzoate, citric acid, sodium citrate, quinoline yellow WS dye (E104) and purified water. See section 2 “Rivastigmine Hexal contains benzoate salt and sodium”

What Rivastigmine HEXAL looks like and contents of the pack
Rivastigmine HEXAL oral solution is supplied as 50 ml or 120 ml of a clear, yellow solution (2.0 mg/ml base) in an amber glass bottle with a child-resistant cap, foam liner, dip tube and self aligning plug. The oral solution is packaged with an oral dosing syringe in a plastic tube container.

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