

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 1.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains rivastigmine hydrogen tartrate equivalent to 1.5 mg rivastigmine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White to almost white powder in a capsule with yellow cap and yellow 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, Nimvastid 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 Nimvastid 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.

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 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 (see sections 4.5 and 4.8).

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

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

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

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

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

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

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. However, Nimvastid 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 torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sultopride, amisulpride, tiapride, veralipride), pimozone, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacin 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 nutritional disorders Very common Common Not known	Anorexia Decreased appetite Dehydration
Psychiatric disorders Common Common Common Common Uncommon Uncommon Very rare Not known	Nightmares Agitation Confusion Anxiety Insomnia Depression Hallucinations Aggression, restlessness

Nervous system disorders Very common Common Common Common Uncommon Rare Very rare	Dizziness Headache Somnolence Tremor Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders Rare Very rare Not known	Angina pectoris Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia) Sick sinus syndrome
Vascular disorders Very rare	Hypertension
Gastrointestinal disorders Very common Very common Very common Common Rare Very rare Very rare Not known	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatitis Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Hepatobiliary disorders Uncommon Not known	Elevated liver function tests Hepatitis
Skin and subcutaneous tissue disorders Common Rare Not known	Hyperhidrosis Rash Pruritus, allergic dermatitis (disseminated)
General disorders and administration site conditions Common Common Uncommon	Fatigue and asthenia Malaise Fall
Investigations Common	Weight loss

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

Table 2

Metabolism and nutritional disorders Common Common	Decreased appetite Dehydration
Psychiatric disorders Common Common Common	Insomnia Anxiety Restlessness

Common Common Not known	Hallucination, visual Depression Aggression
Nervous system disorders Very common Common Common Common Common Common Common Common Uncommon	Tremor Dizziness Somnolence Headache Parkinson's disease (worsening) Bradykinesia Dyskinesia Hypokinesia Cogwheel rigidity Dystonia
Cardiac disorders Common Uncommon Uncommon Not known	Bradycardia Atrial Fibrillation Atrioventricular block Sick sinus syndrome
Vascular disorders Common Uncommon	Hypertension Hypotension
Gastrointestinal disorders Very common Very common Common Common Common	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Salivary hypersecretion
Hepatobiliary disorders Not known	Hepatitis
Skin and subcutaneous tissue disorders Common Not known	Hyperhidrosis Allergic dermatitis (disseminated)
General disorders and administration site conditions Very common Common Common Common	Fall Fatigue and asthenia Gait disturbance Parkinson gait

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

Response Measure	Patients with Clinically Significant Response (%)			
	Intent to Treat		Last Observation Carried Forward	
	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	10*	6	12**	6

improvement on ADAS-Cog with no worsening on CIBIC-Plus and PDS				
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*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 \pm SD	25.4 \pm 9.9	27.4 \pm 10.4	23.1 \pm 10.4	22.5 \pm 10.1
Mean change at 24 weeks \pm SD	1.0 \pm 9.2	-2.1 \pm 8.3	2.6 \pm 7.6	0.1 \pm 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 \pm SD	32.6 \pm 10.4	33.7 \pm 10.3	20.6 \pm 7.9	20.7 \pm 7.9
Mean change at 24 weeks \pm SD	2.6 \pm 9.4	-1.8 \pm 7.2	1.9 \pm 7.7	-0.2 \pm 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% \pm 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 isoenzymes: 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 14C-rivastigmine, renal elimination was rapid and

essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease.

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

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

Capsule content

Microcrystalline cellulose
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell

Titanium dioxide (E171),
Yellow iron oxide (E172),
Gelatine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister pack (PVC/PVDC/Alu-foil): 14, 28, 30, 56, 60 or 112 hard capsules in a box.
HDPE container: 200 or 250 hard capsules in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

14 hard capsules: EU/1/09/525/001
28 hard capsules: EU/1/09/525/002
30 hard capsules: EU/1/09/525/003
56 hard capsules: EU/1/09/525/004
60 hard capsules: EU/1/09/525/005
112 hard capsules: EU/1/09/525/006
200 hard capsules: EU/1/09/525/047
250 hard capsules: EU/1/09/525/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/5/2009
Date of latest renewal: DD month YYYY

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

Nimvastid 3 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains rivastigmine hydrogen tartrate equivalent to 3 mg rivastigmine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White to almost white powder in a capsule with orange cap and orange 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, Nimvastid 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 Nimvastid 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.

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 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 (see sections 4.5 and 4.8).

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

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

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

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

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

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

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. However, Nimvastid 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 torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sultopride, amisulpride, tiapride, veralipride), pimozone, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrine, mizolastin, methadone, pentamidine and moxifloxacin 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 nutritional disorders Very common Common Not known	Anorexia Decreased appetite Dehydration
Psychiatric disorders Common Common Common Common Uncommon Uncommon Very rare Not known	Nightmares Agitation Confusion Anxiety Insomnia Depression Hallucinations Aggression, restlessness

Nervous system disorders Very common Common Common Common Uncommon Rare Very rare	Dizziness Headache Somnolence Tremor Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders Rare Very rare Not known	Angina pectoris Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia) Sick sinus syndrome
Vascular disorders Very rare	Hypertension
Gastrointestinal disorders Very common Very common Very common Common Rare Very rare Very rare Not known	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatitis Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Hepatobiliary disorders Uncommon Not known	Elevated liver function tests Hepatitis
Skin and subcutaneous tissue disorders Common Rare Not known	Hyperhidrosis Rash Pruritus, allergic dermatitis (disseminated)
General disorders and administration site conditions Common Common Uncommon	Fatigue and asthenia Malaise Fall
Investigations Common	Weight loss

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

Table 2

Metabolism and nutritional disorders Common Common	Decreased appetite Dehydration
Psychiatric disorders Common Common Common	Insomnia Anxiety Restlessness

Common Common Not known	Hallucination, visual Depression Aggression
Nervous system disorders Very common Common Common Common Common Common Common Common Uncommon	Tremor Dizziness Somnolence Headache Parkinson's disease (worsening) Bradykinesia Dyskinesia Hypokinesia Cogwheel rigidity Dystonia
Cardiac disorders Common Uncommon Uncommon Not known	Bradycardia Atrial Fibrillation Atrioventricular block Sick sinus syndrome
Vascular disorders Common Uncommon	Hypertension Hypotension
Gastrointestinal disorders Very common Very common Common Common Common	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Salivary hypersecretion
Hepatobiliary disorders Not known	Hepatitis
Skin and subcutaneous tissue disorders Common Not known	Hyperhidrosis Allergic dermatitis (disseminated)
General disorders and administration site conditions Very common Common Common Common	Fall Fatigue and asthenia Gait disturbance Parkinson gait

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

Response Measure	Patients with Clinically Significant Response (%)			
	Intent to Treat		Last Observation Carried Forward	
	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	10*	6	12**	6

improvement on ADAS-Cog with no worsening on CIBIC-Plus and PDS				
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*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 \pm SD	25.4 \pm 9.9	27.4 \pm 10.4	23.1 \pm 10.4	22.5 \pm 10.1
Mean change at 24 weeks \pm SD	1.0 \pm 9.2	-2.1 \pm 8.3	2.6 \pm 7.6	0.1 \pm 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 \pm SD	32.6 \pm 10.4	33.7 \pm 10.3	20.6 \pm 7.9	20.7 \pm 7.9
Mean change at 24 weeks \pm SD	2.6 \pm 9.4	-1.8 \pm 7.2	1.9 \pm 7.7	-0.2 \pm 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% \pm 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 isoenzymes: 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 14C-rivastigmine, renal elimination was rapid and

essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease.

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

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

Capsule content

Microcrystalline cellulose
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell

Titanium dioxide (E171),
Yellow iron oxide (E172),
Red iron oxide (E172)
Gelatine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister pack (PVC/PVDC/Alu-foil): 28, 30, 56, 60 or 112 hard capsules in a box.
HDPE container: 200 or 250 hard capsules in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

28 hard capsules: EU/1/09/525/008
30 hard capsules: EU/1/09/525/009
56 hard capsules: EU/1/09/525/010
60 hard capsules: EU/1/09/525/011
112 hard capsules: EU/1/09/525/012
200 hard capsules: EU/1/09/525/048
250 hard capsules: EU/1/09/525/013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/5/2009
Date of latest renewal: DD month YYYY

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

Nimvastid 4.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains rivastigmine hydrogen tartrate equivalent to 4.5 mg rivastigmine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White to almost white powder in a capsule with brownish red cap and brownish red 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, Nimvastid 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 Nimvastid 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.

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 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 (see sections 4.5 and 4.8).

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

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

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

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

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

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

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. However, Nimvastid 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 torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sultopride, amisulpride, tiapride, veralipride), pimozone, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacin 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 nutritional disorders Very common Common Not known	Anorexia Decreased appetite Dehydration
Psychiatric disorders Common Common Common Common Uncommon Uncommon Very rare Not known	Nightmares Agitation Confusion Anxiety Insomnia Depression Hallucinations Aggression, restlessness

Nervous system disorders Very common Common Common Common Uncommon Rare Very rare	Dizziness Headache Somnolence Tremor Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders Rare Very rare Not known	Angina pectoris Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia) Sick sinus syndrome
Vascular disorders Very rare	Hypertension
Gastrointestinal disorders Very common Very common Very common Common Rare Very rare Very rare Not known	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatitis Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Hepatobiliary disorders Uncommon Not known	Elevated liver function tests Hepatitis
Skin and subcutaneous tissue disorders Common Rare Not known	Hyperhidrosis Rash Pruritus, allergic dermatitis (disseminated)
General disorders and administration site conditions Common Common Uncommon	Fatigue and asthenia Malaise Fall
Investigations Common	Weight loss

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

Table 2

Metabolism and nutritional disorders Common Common	Decreased appetite Dehydration
Psychiatric disorders Common Common Common	Insomnia Anxiety Restlessness

Common Common Not known	Hallucination, visual Depression Aggression
Nervous system disorders Very common Common Common Common Common Common Common Common Uncommon	Tremor Dizziness Somnolence Headache Parkinson's disease (worsening) Bradykinesia Dyskinesia Hypokinesia Cogwheel rigidity Dystonia
Cardiac disorders Common Uncommon Uncommon Not known	Bradycardia Atrial Fibrillation Atrioventricular block Sick sinus syndrome
Vascular disorders Common Uncommon	Hypertension Hypotension
Gastrointestinal disorders Very common Very common Common Common Common	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Salivary hypersecretion
Hepatobiliary disorders Not known	Hepatitis
Skin and subcutaneous tissue disorders Common Not known	Hyperhidrosis Allergic dermatitis (disseminated)
General disorders and administration site conditions Very common Common Common Common	Fall Fatigue and asthenia Gait disturbance Parkinson gait

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

Response Measure	Patients with Clinically Significant Response (%)			
	Intent to Treat		Last Observation Carried Forward	
	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	10*	6	12**	6

improvement on ADAS-Cog with no worsening on CIBIC-Plus and PDS				
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*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 \pm SD	25.4 \pm 9.9	27.4 \pm 10.4	23.1 \pm 10.4	22.5 \pm 10.1
Mean change at 24 weeks \pm SD	1.0 \pm 9.2	-2.1 \pm 8.3	2.6 \pm 7.6	0.1 \pm 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 \pm SD	32.6 \pm 10.4	33.7 \pm 10.3	20.6 \pm 7.9	20.7 \pm 7.9
Mean change at 24 weeks \pm SD	2.6 \pm 9.4	-1.8 \pm 7.2	1.9 \pm 7.7	-0.2 \pm 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% \pm 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 isoenzymes: 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 14C-rivastigmine, renal elimination was rapid and

essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease.

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

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

Capsule content

Microcrystalline cellulose
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell

Titanium dioxide (E171),
Yellow iron oxide (E172),
Red iron oxide (E172)
Gelatine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister pack (PVC/PVDC/Alu-foil): 28, 30, 56, 60 or 112 hard capsules in a box.
HDPE container: 200 or 250 hard capsules in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

28 hard capsules: EU/1/09/525/014
30 hard capsules: EU/1/09/525/015
56 hard capsules: EU/1/09/525/016
60 hard capsules: EU/1/09/525/017
112 hard capsules: EU/1/09/525/018
200 hard capsules: EU/1/09/525/049
250 hard capsules: EU/1/09/525/019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/5/2009
Date of latest renewal: DD month YYYY

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

Nimvastid 6 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains rivastigmine hydrogen tartrate equivalent to 6 mg rivastigmine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

White to almost white powder in a capsule with a brownish red cap and orange 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, Nimvastid 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 Nimvastid 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.

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 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 (see sections 4.5 and 4.8).

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

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

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

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

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

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

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. However, Nimvastid 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 torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sultopride, amisulpride, tiapride, veralipride), pimozone, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacin 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 nutritional disorders Very common Common Not known	Anorexia Decreased appetite Dehydration
Psychiatric disorders Common Common Common Common Uncommon Uncommon Very rare Not known	Nightmares Agitation Confusion Anxiety Insomnia Depression Hallucinations Aggression, restlessness

Nervous system disorders Very common Common Common Common Uncommon Rare Very rare	Dizziness Headache Somnolence Tremor Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders Rare Very rare Not known	Angina pectoris Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia) Sick sinus syndrome
Vascular disorders Very rare	Hypertension
Gastrointestinal disorders Very common Very common Very common Common Rare Very rare Very rare Not known	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatitis Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Hepatobiliary disorders Uncommon Not known	Elevated liver function tests Hepatitis
Skin and subcutaneous tissue disorders Common Rare Not known	Hyperhidrosis Rash Pruritus, allergic dermatitis (disseminated)
General disorders and administration site conditions Common Common Uncommon	Fatigue and asthenia Malaise Fall
Investigations Common	Weight loss

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

Table 2

Metabolism and nutritional disorders Common Common	Decreased appetite Dehydration
Psychiatric disorders Common Common Common	Insomnia Anxiety Restlessness

Common Common Not known	Hallucination, visual Depression Aggression
Nervous system disorders Very common Common Common Common Common Common Common Common Uncommon	Tremor Dizziness Somnolence Headache Parkinson's disease (worsening) Bradykinesia Dyskinesia Hypokinesia Cogwheel rigidity Dystonia
Cardiac disorders Common Uncommon Uncommon Not known	Bradycardia Atrial Fibrillation Atrioventricular block Sick sinus syndrome
Vascular disorders Common Uncommon	Hypertension Hypotension
Gastrointestinal disorders Very common Very common Common Common Common	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Salivary hypersecretion
Hepatobiliary disorders Not known	Hepatitis
Skin and subcutaneous tissue disorders Common Not known	Hyperhidrosis Allergic dermatitis (disseminated)
General disorders and administration site conditions Very common Common Common Common	Fall Fatigue and asthenia Gait disturbance Parkinson gait

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

Response Measure	Patients with Clinically Significant Response (%)			
	Intent to Treat		Last Observation Carried Forward	
	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	10*	6	12**	6

improvement on ADAS-Cog with no worsening on CIBIC-Plus and PDS				
-----------------------------------------------------------------	--	--	--	--

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

Clinical studies in dementia associated with Parkinson's disease

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

Table 5

Dementia associated with Parkinson's Disease	ADAS-Cog Rivastigmine	ADAS-Cog Placebo	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 \pm SD	25.4 \pm 9.9	27.4 \pm 10.4	23.1 \pm 10.4	22.5 \pm 10.1
Mean change at 24 weeks \pm SD	1.0 \pm 9.2	-2.1 \pm 8.3	2.6 \pm 7.6	0.1 \pm 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 \pm SD	32.6 \pm 10.4	33.7 \pm 10.3	20.6 \pm 7.9	20.7 \pm 7.9
Mean change at 24 weeks \pm SD	2.6 \pm 9.4	-1.8 \pm 7.2	1.9 \pm 7.7	-0.2 \pm 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% \pm 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 isoenzymes: 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 14C-rivastigmine, renal elimination was rapid and

essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease.

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

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

Capsule content

Microcrystalline cellulose
Hypromellose
Silica, colloidal anhydrous
Magnesium stearate

Capsule shell

Titanium dioxide (E171),
Yellow iron oxide (E172),
Red iron oxide (E172)
Gelatine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister pack (PVC/PVDC/Alu-foil): 28, 30, 56, 60 or 112 hard capsules in a box.
HDPE container: 200 or 250 hard capsules in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

28 hard capsules: EU/1/09/525/020
30 hard capsules: EU/1/09/525/021
56 hard capsules: EU/1/09/525/022
60 hard capsules: EU/1/09/525/023
112 hard capsules: EU/1/09/525/024
200 hard capsules: EU/1/09/525/050
250 hard capsules: EU/1/09/525/025

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/5/2009
Date of latest renewal: DD month YYYY

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

Nimvastid 1.5 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains rivastigmine hydrogen tartrate equivalent to 1.5 mg rivastigmine.

Excipient with known effect:

Each orodispersible tablet contains 5.25 µg sorbitol E420.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet.

The tablets are round and white.

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.

Nimvastid orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister.

Rivastigmine orodispersible tablet is bioequivalent to rivastigmine capsules, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as rivastigmine capsules. Rivastigmine orodispersible tablets may be used as an alternative to rivastigmine capsules.

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, Nimvastid orodispersible tablets 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 Nimvastid 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.

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 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 (see sections 4.5 and 4.8).

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

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

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

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

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

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

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. However, Nimvastid 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.

Nimvastid contains sorbitol E420. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 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 moxifloxacin 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 nutritional disorders Very common Common Not known	Anorexia Decreased appetite Dehydration

Psychiatric disorders Common Common Common Common Uncommon Uncommon Very rare Not known	Nightmares Agitation Confusion Anxiety Insomnia Depression Hallucinations Aggression, restlessness
Nervous system disorders Very common Common Common Common Uncommon Rare Very rare	Dizziness Headache Somnolence Tremor Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders Rare Very rare Not known	Angina pectoris Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia) Sick sinus syndrome
Vascular disorders Very rare	Hypertension
Gastrointestinal disorders Very common Very common Very common Common Rare Very rare Very rare Not known	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatitis Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Hepatobiliary disorders Uncommon Not known	Elevated liver function tests Hepatitis
Skin and subcutaneous tissue disorders Common Rare Not known	Hyperhidrosis Rash Pruritus, allergic dermatitis (disseminated)
General disorders and administration site conditions Common Common Uncommon	Fatigue and asthenia Malaise Fall
Investigations Common	Weight loss

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

Table 2

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

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

Response Measure	Patients with Clinically Significant Response (%)			
	Intent to Treat		Last Observation Carried Forward	
	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 p-value versus placebo		2.88 ¹ <0.001 ¹		n/a 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 p-value versus placebo		3.54 ¹ <0.001 ¹		n/a <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
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	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

Rivastigmine orodispersible tablet is bioequivalent to rivastigmine capsules, with a similar rate and extent of absorption. Rivastigmine orodispersible tablets may be used as an alternative to rivastigmine capsules.

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 isoenzymes: 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 ¹⁴C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease.

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

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 10⁴ 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

Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Spearmint flavour (peppermint oil, maize maltodextrin)
Peppermint flavour (maltodextrine, gum arabic, sorbitol E420, corn mint oil, L-menthol)
Crospovidone
Calcium silicate
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1 or 112 x 1 tablet in OPA/Alu/PVC foil film and PET/Alu peel off foil perforated unit dose blister packs in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

14 x 1 orodispersible tablet:EU/1/09/525/026
28 x 1 orodispersible tablet:EU/1/09/525/027
30 x 1 orodispersible tablet:EU/1/09/525/028
56 x 1 orodispersible tablet:EU/1/09/525/029
60 x 1 orodispersible tablet:EU/1/09/525/030
112 x 1 orodispersible tablet:EU/1/09/525/031

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/5/2009
Date of latest renewal: DD month YYYY

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

Nimvastid 3 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains rivastigmine hydrogen tartrate equivalent to 3 mg rivastigmine.

Excipient with known effect:

Each orodispersible tablet contains 10.5 µg sorbitol E420.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet.

The tablets are round and white.

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.

Nimvastid orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister.

Rivastigmine orodispersible tablet is bioequivalent to rivastigmine capsules, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as rivastigmine capsules. Rivastigmine orodispersible tablets may be used as an alternative to rivastigmine capsules.

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, Nimvastid orodispersible tablets 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 Nimvastid 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.

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 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 (see sections 4.5 and 4.8).

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

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

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

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

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

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

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. However, Nimvastid 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.

Nimvastid contains sorbitol E420. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 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 moxifloxacin 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 nutritional disorders Very common Common Not known	Anorexia Decreased appetite Dehydration

Psychiatric disorders Common Common Common Common Uncommon Uncommon Very rare Not known	Nightmares Agitation Confusion Anxiety Insomnia Depression Hallucinations Aggression, restlessness
Nervous system disorders Very common Common Common Common Uncommon Rare Very rare	Dizziness Headache Somnolence Tremor Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders Rare Very rare Not known	Angina pectoris Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia) Sick sinus syndrome
Vascular disorders Very rare	Hypertension
Gastrointestinal disorders Very common Very common Very common Common Rare Very rare Very rare Not known	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatitis Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Hepatobiliary disorders Uncommon Not known	Elevated liver function tests Hepatitis
Skin and subcutaneous tissue disorders Common Rare Not known	Hyperhidrosis Rash Pruritus, allergic dermatitis (disseminated)
General disorders and administration site conditions Common Common Uncommon	Fatigue and asthenia Malaise Fall
Investigations Common	Weight loss

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

Table 2

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

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

Response Measure	Patients with Clinically Significant Response (%)			
	Intent to Treat		Last Observation Carried Forward	
	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 p-value versus placebo		2.88 ¹ <0.001 ¹		n/a 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 p-value versus placebo		3.54 ¹ <0.001 ¹		n/a <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

Rivastigmine orodispersible tablet is bioequivalent to rivastigmine capsules, with a similar rate and extent of absorption. Rivastigmine orodispersible tablets may be used as an alternative to rivastigmine capsules.

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 isoenzymes: 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 ¹⁴C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease.

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

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

Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Spearmint flavour (peppermint oil, maize maltodextrin)
Peppermint flavour (maltodextrine, gum arabic, sorbitol E420, corn mint oil, L-menthol)
Crospovidone
Calcium silicate
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

28 x 1, 30 x 1, 56 x 1, 60 x 1 or 112 x 1 tablet in OPA/Alu/PVC foil film and PET/Alu peel off foil perforated unit dose blister packs in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

28 x 1 orodispersible tablet:EU/1/09/525/032
30 x 1 orodispersible tablet:EU/1/09/525/033
56 x 1 orodispersible tablet:EU/1/09/525/034
60 x 1 orodispersible tablet:EU/1/09/525/035
112 x 1 orodispersible tablet:EU/1/09/525/036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/5/2009
Date of latest renewal: DD month YYYY

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

Nimvastid 4.5 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains rivastigmine hydrogen tartrate equivalent to 4.5 mg rivastigmine.

Excipient with known effect:

Each orodispersible tablet contains 15.75 µg sorbitol E420.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet.

The tablets are round and white.

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.

Nimvastid orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister.

Rivastigmine orodispersible tablet is bioequivalent to rivastigmine capsules, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as rivastigmine capsules. Rivastigmine orodispersible tablets may be used as an alternative to rivastigmine capsules.

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, Nimvastid orodispersible tablets 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 Nimvastid 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.

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 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 (see sections 4.5 and 4.8).

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

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

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

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

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

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

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. However, Nimvastid 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.

Nimvastid contains sorbitol E420. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 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 moxifloxacin 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 nutritional disorders Very common Common Not known	Anorexia Decreased appetite Dehydration

Psychiatric disorders Common Common Common Common Uncommon Uncommon Very rare Not known	Nightmares Agitation Confusion Anxiety Insomnia Depression Hallucinations Aggression, restlessness
Nervous system disorders Very common Common Common Common Uncommon Rare Very rare	Dizziness Headache Somnolence Tremor Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders Rare Very rare Not known	Angina pectoris Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia) Sick sinus syndrome
Vascular disorders Very rare	Hypertension
Gastrointestinal disorders Very common Very common Very common Common Rare Very rare Very rare Not known	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatitis Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Hepatobiliary disorders Uncommon Not known	Elevated liver function tests Hepatitis
Skin and subcutaneous tissue disorders Common Rare Not known	Hyperhidrosis Rash Pruritus, allergic dermatitis (disseminated)
General disorders and administration site conditions Common Common Uncommon	Fatigue and asthenia Malaise Fall
Investigations Common	Weight loss

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

Table 2

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

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

Response Measure	Patients with Clinically Significant Response (%)			
	Intent to Treat		Last Observation Carried Forward	
	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 p-value versus placebo		2.88 ¹ <0.001 ¹		n/a 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 p-value versus placebo		3.54 ¹ <0.001 ¹		n/a <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
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	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

Rivastigmine orodispersible tablet is bioequivalent to rivastigmine capsules, with a similar rate and extent of absorption. Rivastigmine orodispersible tablets may be used as an alternative to rivastigmine capsules.

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 isoenzymes: 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 ¹⁴C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease.

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

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 10⁴ 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

Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Spearmint flavour (peppermint oil, maize maltodextrin)
Peppermint flavour (maltodextrine, gum arabic, sorbitol E420, corn mint oil, L-menthol)
Crospovidone
Calcium silicate
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

28 x 1, 30 x 1, 56 x 1, 60 x 1 or 112 x 1 tablet in OPA/Alu/PVC foil film and PET/Alu peel off foil perforated unit dose blister packs in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

28 x 1 orodispersible tablet:EU/1/09/525/037
30 x 1 orodispersible tablet:EU/1/09/525/038
56 x 1 orodispersible tablet:EU/1/09/525/039
60 x 1 orodispersible tablet:EU/1/09/525/040
112 x 1 orodispersible tablet:EU/1/09/525/041

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/5/2009
Date of latest renewal: DD month YYYY

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

Nimvastid 6 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains rivastigmine hydrogen tartrate equivalent to 6 mg rivastigmine.

Excipient with known effect:

Each orodispersible tablet contains 21 µg sorbitol E420.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet.

The tablets are round and white.

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.

Nimvastid orodispersible tablet should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister.

Rivastigmine orodispersible tablet is bioequivalent to rivastigmine capsules, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as rivastigmine capsules. Rivastigmine orodispersible tablets may be used as an alternative to rivastigmine capsules.

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, Nimvastid orodispersible tablets 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 Nimvastid 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.

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 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 (see sections 4.5 and 4.8).

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

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

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

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

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

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

Special populations

Patients with clinically significant renal or hepatic impairment might experience more adverse reactions (see sections 4.2 and 5.2). Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. However, Nimvastid 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.

Nimvastid contains sorbitol E420. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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 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 moxifloxacin 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 nutritional disorders Very common Common Not known	Anorexia Decreased appetite Dehydration

Psychiatric disorders Common Common Common Common Uncommon Uncommon Very rare Not known	Nightmares Agitation Confusion Anxiety Insomnia Depression Hallucinations Aggression, restlessness
Nervous system disorders Very common Common Common Common Uncommon Rare Very rare	Dizziness Headache Somnolence Tremor Syncope Seizures Extrapyramidal symptoms (including worsening of Parkinson's disease)
Cardiac disorders Rare Very rare Not known	Angina pectoris Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia) Sick sinus syndrome
Vascular disorders Very rare	Hypertension
Gastrointestinal disorders Very common Very common Very common Common Rare Very rare Very rare Not known	Nausea Vomiting Diarrhoea Abdominal pain and dyspepsia Gastric and duodenal ulcers Gastrointestinal haemorrhage Pancreatitis Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).
Hepatobiliary disorders Uncommon Not known	Elevated liver function tests Hepatitis
Skin and subcutaneous tissue disorders Common Rare Not known	Hyperhidrosis Rash Pruritus, allergic dermatitis (disseminated)
General disorders and administration site conditions Common Common Uncommon	Fatigue and asthenia Malaise Fall
Investigations Common	Weight loss

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

Table 2

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

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

Response Measure	Patients with Clinically Significant Response (%)			
	Intent to Treat		Last Observation Carried Forward	
	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 p-value versus placebo		2.88 ¹ <0.001 ¹		n/a 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 p-value versus placebo		3.54 ¹ <0.001 ¹		n/a <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
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	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

Rivastigmine orodispersible tablet is bioequivalent to rivastigmine capsules, with a similar rate and extent of absorption. Rivastigmine orodispersible tablets may be used as an alternative to rivastigmine capsules.

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 isoenzymes: 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 ¹⁴C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces. There is no accumulation of rivastigmine or the decarbamylated metabolite in patients with Alzheimer's disease.

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

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 10⁴ 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

Mannitol
Microcrystalline cellulose
Hydroxypropylcellulose
Spearmint flavour (peppermint oil, maize maltodextrin)
Peppermint flavour (maltodextrine, gum arabic, sorbitol E420, corn mint oil, L-menthol)
Crospovidone
Calcium silicate
Magnesium stearate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

28 x 1, 30 x 1, 56 x 1, 60 x 1 or 112 x 1 tablet in OPA/Alu/PVC foil film and PET/Alu peel off foil perforated unit dose blister packs in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

28 x 1 orodispersible tablet:EU/1/09/525/042
30 x 1 orodispersible tablet:EU/1/09/525/043
56 x 1 orodispersible tablet:EU/1/09/525/044
60 x 1 orodispersible tablet:EU/1/09/525/045
112 x 1 orodispersible tablet:EU/1/09/525/046

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/5/2009
Date of latest renewal: DD month YYYY

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>

ANNEX II

- A. MANUFACTURER 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 REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

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 Characteristic, Section 4.2.)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports 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 REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON FOR BLISTERS AND CONTAINER, AND LABEL FOR CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 1.5 mg hard capsules

Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains rivastigmine hydrogen tartrate equivalent to 1.5 mg rivastigmine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

Blister:

14 hard capsules

28 hard capsules

30 hard capsules

56 hard capsules

60 hard capsules

112 hard capsules

Container:

200 hard capsules

250 hard capsules

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

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

14 hard capsules: EU/1/09/525/001
28 hard capsules: EU/1/09/525/002
30 hard capsules: EU/1/09/525/003
56 hard capsules: EU/1/09/525/004
60 hard capsules: EU/1/09/525/005
112 hard capsules: EU/1/09/525/006
200 hard capsules: EU/1/09/525/047
250 hard capsules: EU/1/09/525/007

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nimvastid 1.5 mg (on carton label only)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

(on carton label only)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

(on carton label only)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 1.5 mg hard capsules

Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON FOR BLISTERS AND CONTAINER, AND LABEL FOR CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 3 mg hard capsules

Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains rivastigmine hydrogen tartrate equivalent to 3 mg rivastigmine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

Blister:

28 hard capsules

30 hard capsules

56 hard capsules

60 hard capsules

112 hard capsules

Container:

200 hard capsules

250 hard capsules

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

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

28 hard capsules: EU/1/09/525/008
30 hard capsules: EU/1/09/525/009
56 hard capsules: EU/1/09/525/010
60 hard capsules: EU/1/09/525/011
112 hard capsules: EU/1/09/525/012
200 hard capsules: EU/1/09/525/048
250 hard capsules: EU/1/09/525/013

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nimvastid 3mg (on carton label only)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

(on carton label only)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:

NN:

(on carton label only)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 3 mg hard capsules

Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON FOR BLISTERS AND CONTAINER, AND LABEL FOR CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 4.5 mg hard capsules

Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains rivastigmine hydrogen tartrate equivalent to 4.5 mg rivastigmine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

Blister:

28 hard capsules

30 hard capsules

56 hard capsules

60 hard capsules

112 hard capsules

Container:

200 hard capsules

250 hard capsules

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

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

28 hard capsules: EU/1/09/525/014
30 hard capsules: EU/1/09/525/015
56 hard capsules: EU/1/09/525/016
60 hard capsules: EU/1/09/525/017
112 hard capsules: EU/1/09/525/018
200 hard capsules: EU/1/09/525/049
250 hard capsules: EU/1/09/525/019

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nimvastid 4.5 mg (on carton label only)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

(on carton label only)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:

NN:

(on carton label only)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 4.5 mg hard capsules

Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON FOR BLISTERS AND CONTAINER, AND LABEL FOR CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 6 mg hard capsules

Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains rivastigmine hydrogen tartrate equivalent to 6 mg rivastigmine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

Blister:

28 hard capsules

30 hard capsules

56 hard capsules

60 hard capsules

112 hard capsules

Container:

200 hard capsules

250 hard capsules

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

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

28 hard capsules: EU/1/09/525/020
30 hard capsules: EU/1/09/525/021
56 hard capsules: EU/1/09/525/022
60 hard capsules: EU/1/09/525/023
112 hard capsules: EU/1/09/525/024
200 hard capsules: EU/1/09/525/050
250 hard capsules: EU/1/09/525/025

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nimvastid 6 mg (on carton label only)

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

(on carton label only)

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

(on carton label only)

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 6 mg hard capsules

Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 1.5 mg orodispersible tablets

Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains rivastigmine hydrogen tartrate equivalent to 1.5 mg rivastigmine.

3. LIST OF EXCIPIENTS

Excipient: sorbitol E420.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

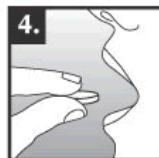
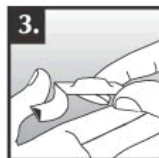
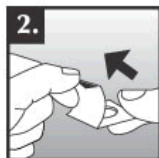
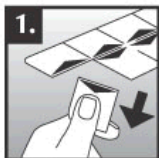
14 x 1 orodispersible tablet
28 x 1 orodispersible tablet
30 x 1 orodispersible tablet
56 x 1 orodispersible tablet
60 x 1 orodispersible tablet
112 x 1 orodispersible tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

Do not handle the tablets with wet hands as the tablets may break up.

1. Hold the blister strip at the edges and separate one blister cell from the rest of the strip by gently tearing along the perforations around it,
2. Pull up the edge of the foil and peel foil off completely,
3. Tip the tablet out onto your hand.
4. Put the tablet on the tongue as soon as it is removed from the packaging.



Dissolve the tablet in the mouth and swallow it with or without water.

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

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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

14 x 1 orodispersible tablet:EU/1/09/525/026
28 x 1 orodispersible tablet:EU/1/09/525/027
30 x 1 orodispersible tablet:EU/1/09/525/028
56 x 1 orodispersible tablet:EU/1/09/525/029
60 x 1 orodispersible tablet:EU/1/09/525/030
112 x 1 orodispersible tablet:EU/1/09/525/031

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nimvastid 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 1.5 mg orodispersible tablets

Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

1. Tear.
2. Peel.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 3 mg orodispersible tablets

Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains rivastigmine hydrogen tartrate equivalent to 3 mg rivastigmine.

3. LIST OF EXCIPIENTS

Excipient: sorbitol E420.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

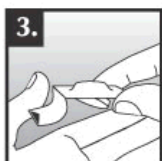
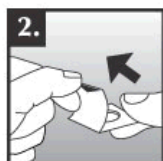
28 x 1 orodispersible tablet
30 x 1 orodispersible tablet
56 x 1 orodispersible tablet
60 x 1 orodispersible tablet
112 x 1 orodispersible tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

Do not handle the tablets with wet hands as the tablets may break up.

1. Hold the blister strip at the edges and separate one blister cell from the rest of the strip by gently tearing along the perforations around it,
2. Pull up the edge of the foil and peel foil off completely,
3. Tip the tablet out onto your hand.
4. Put the tablet on the tongue as soon as it is removed from the packaging.



Dissolve the tablet in the mouth and swallow it with or without water.

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

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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

28 x 1 orodispersible tablet:EU/1/09/525/032
30 x 1 orodispersible tablet:EU/1/09/525/033
56 x 1 orodispersible tablet:EU/1/09/525/034
60 x 1 orodispersible tablet:EU/1/09/525/035
112 x 1 orodispersible tablet:EU/1/09/525/036

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nimvastid 3 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 3 mg orodispersible tablets

Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

1. Tear.
2. Peel.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 4.5 mg orodispersible tablets

Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains rivastigmine hydrogen tartrate equivalent to 4.5 mg rivastigmine.

3. LIST OF EXCIPIENTS

Excipient: sorbitol E420.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

28 x 1 orodispersible tablet

30 x 1 orodispersible tablet

56 x 1 orodispersible tablet

60 x 1 orodispersible tablet

112 x 1 orodispersible tablet

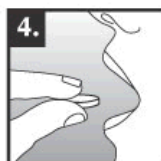
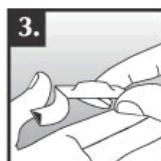
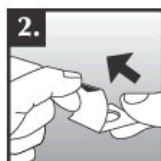
5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

Do not handle the tablets with wet hands as the tablets may break up.

1. Hold the blister strip at the edges and separate one blister cell from the rest of the strip by gently tearing along the perforations around it,
2. Pull up the edge of the foil and peel foil off completely,
3. Tip the tablet out onto your hand.
4. Put the tablet on the tongue as soon as it is removed from the packaging.



Dissolve the tablet in the mouth and swallow it with or without water.

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

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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

28 x 1 orodispersible tablet:EU/1/09/525/037
30 x 1 orodispersible tablet:EU/1/09/525/038
56 x 1 orodispersible tablet:EU/1/09/525/039
60 x 1 orodispersible tablet:EU/1/09/525/040
112 x 1 orodispersible tablet:EU/1/09/525/041

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nimvastid 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 4.5 mg orodispersible tablets

Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

1. Tear.
2. Peel.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 6 mg orodispersible tablets

Rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains rivastigmine hydrogen tartrate equivalent to 6 mg rivastigmine.

3. LIST OF EXCIPIENTS

Excipient: sorbitol E420.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

28 x 1 orodispersible tablet

30 x 1 orodispersible tablet

56 x 1 orodispersible tablet

60 x 1 orodispersible tablet

112 x 1 orodispersible tablet

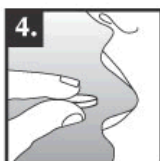
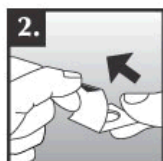
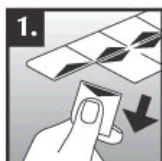
5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

Do not handle the tablets with wet hands as the tablets may break up.

1. Hold the blister strip at the edges and separate one blister cell from the rest of the strip by gently tearing along the perforations around it,
2. Pull up the edge of the foil and peel foil off completely,
3. Tip the tablet out onto your hand.
4. Put the tablet on the tongue as soon as it is removed from the packaging.



Dissolve the tablet in the mouth and swallow it with or without water.

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

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

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

12. MARKETING AUTHORISATION NUMBER(S)

28 x 1 orodispersible tablet:EU/1/09/525/042
30 x 1 orodispersible tablet:EU/1/09/525/043
56 x 1 orodispersible tablet:EU/1/09/525/044
60 x 1 orodispersible tablet:EU/1/09/525/045
112 x 1 orodispersible tablet:EU/1/09/525/046

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Nimvastid 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Nimvastid 6 mg orodispersible tablets

Rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

1. Tear.
2. Peel.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Nimvastid 1.5 mg hard capsules

Nimvastid 3 mg hard capsules

Nimvastid 4.5 mg hard capsules

Nimvastid 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Nimvastid is and what it is used for
2. What you need to know before you take Nimvastid
3. How to take Nimvastid
4. Possible side effects
5. How to store Nimvastid
6. Contents of the pack and other information

1. What Nimvastid is and what it is used for

The active substance of Nimvastid 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, Nimvastid 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.

Nimvastid 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 Nimvastid

Do not take Nimvastid

- if you are allergic to rivastigmine (the active substance in Nimvastid) or to any of the other ingredients of this medicine (listed in section 6).
- if you have a skin reaction spreading beyond the patch size, if there is a more intense local reaction (such as blisters, increasing skin inflammation, swelling) and if it does not improve within 48 hours after removal of the transdermal patch.

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

Warnings and precautions

Talk to your doctor before taking Nimvastid:

- if you have, or have ever had, irregular or slow heartbeat.
- if you have, or have ever had, an active stomach ulcer.
- if you have, or have ever had, difficulties in passing urine.
- if you have, or have ever had, seizures.
- if you have, or have ever had, asthma or severe respiratory disease.
- if you have, or have ever had impaired kidney function.
- if you have, or have ever had, impaired liver function.
- if you suffer from trembling.
- if you have a low body weight.
- if you have gastrointestinal reactions such as feeling sick (nausea), 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 Nimvastid 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 Nimvastid in the paediatric population in the treatment of Alzheimer's disease.

Other medicines and Nimvastid

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

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

Nimvastid 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 Nimvastid, tell your doctor before you are given any anaesthetics, because Nimvastid may exaggerate the effects of some muscle relaxants during anaesthesia.

Caution when Nimvastid 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.

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 Nimvastid must be assessed against the possible effects on your unborn child. Nimvastid should not be used during pregnancy unless clearly necessary.

You should not breast-feed during treatment with Nimvastid.

Driving and using machines

Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely. Nimvastid 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 Nimvastid

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

How to start treatment

Your doctor will tell you what dose of Nimvastid 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 Nimvastid 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 Nimvastid.
- To benefit from your medicine, take it every day.
- Take Nimvastid 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 Nimvastid than you should

If you accidentally take more Nimvastid than you should, inform your doctor. You may require medical attention. Some people who have accidentally taken too much Nimvastid 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 Nimvastid

If you find you have forgotten to take your dose of Nimvastid, 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

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 rivastigmine 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, pharmacist or nurse. 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 Nimvastid

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

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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. Contents of the pack and other information

What Nimvastid contains

- The active substance is rivastigmine hydrogen tartrate.
Each hard capsule contains rivastigmine hydrogen tartrate equivalent to 1.5 mg, 3 mg, 4.5 mg or 6 mg rivastigmine.
- The other ingredients for Nimvastid 1.5 mg capsules are microcrystalline cellulose, hypromellose, colloidal anhydrous silica, magnesium stearate in the capsule content, and titanium dioxide (E171), yellow iron oxide (E172) and gelatine in the capsule shell.
- The other ingredients for Nimvastid 3 mg, 4.5 mg and 6 mg capsules are microcrystalline cellulose, hypromellose, colloidal anhydrous silica, magnesium stearate in the capsule content,

and titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172) and gelatine in the capsule shell.

What Nimvastid looks like and contents of the pack

Nimvastid 1.5 mg hard capsules, which contain a white to almost white powder, have a yellow cap and yellow body.

Nimvastid 3 mg hard capsules, which contain a white to almost white powder, have an orange cap and orange body.

Nimvastid 4.5 mg hard capsules, which contain a white to almost white powder, have a brownish red cap and brownish red body.

Nimvastid 6 mg hard capsules, which contain a white to almost white powder, have a brownish red cap and orange body.

Blister pack (PVC/PVDC/Alu-foil): boxes of 14 (only for 1.5 mg), 28, 30, 56, 60 or 112 hard capsules are available.

HDPE container: boxes of 200 or 250 hard capsules are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien

KRKA Belgium, SA.

Tél/Tel: +32 (0) 487 50 73 62

Lietuva

UAB KRKA Lietuva

Tel: + 370 5 236 27 40

България

КРКА България ЕООД

Тел.: + 359 (02) 962 34 50

Luxembourg/Luxemburg

KRKA Belgium, SA.

Tél/Tel: +32 (0) 487 50 73 62 (BE)

Česká republika

KRKA ČR, s.r.o.

Tel: + 420 (0) 221 115 150

Magyarország

KRKA Magyarország Kereskedelmi Kft.

Tel.: + 361 (0) 355 8490

Danmark

KRKA Sverige AB

Tlf: + 46 (0)8 643 67 66 (SE)

Malta

E.J. Busuttil Ltd.

Tel: +356 21 445 885

Deutschland

TAD Pharma GmbH

Tel: + 49 (0) 4721 606-0

Nederland

KRKA Belgium, SA.

Tel: +32 (0) 487 50 73 62 (BE)

Eesti

KRKA, d.d., Novo mesto Eesti filiaal

Tel: + 372 (0) 6 671 658

Norge

KRKA Sverige AB

Tlf: + 46 (0)8 643 67 66 (SE)

Ελλάδα

QUALIA PHARMA S.A.

Τηλ: +30 210 6256177

Österreich

KRKA Pharma GmbH, Wien

Tel: + 43 (0)1 66 24 300

España

KRKA Farmacéutica, S.L.
Tel: + 34 911 61 03 81

France

KRKA France Eurl
Tél: + 33 (0)1 57 40 82 25

Hrvatska

KRKA - FARMA d.o.o.
Tel: + 385 1 6312 100

Ireland

KRKA Pharma Dublin, Ltd.
Tel: + 353 1 293 91 80

Ísland

KRKA Sverige AB
Sími: + 46 (0)8 643 67 66 (SE)

Italia

KRKA Farmaceutici Milano S.r.l.
Tel: + 39 02 3300 8841

Κύπρος

Kipa Pharmacal Ltd.
Τηλ: + 357 24 651 882

Latvija

KRKA Latvija SIA
Tel: + 371 6 733 86 10

Polska

KRKA-POLSKA Sp. z o.o.
Tel.: + 48 (0)22 573 7500

Portugal

KRKA Farmacéutica, Sociedade Unipessoal Lda.
Tel: + 351 (0)21 46 43 650

România

KRKA Romania S.R.L., Bucharest
Tel: + 4 021 310 66 05

Slovenija

KRKA, d.d., Novo mesto
Tel: + 386 (0) 1 47 51 100

Slovenská republika

KRKA Slovensko, s.r.o.,
Tel: + 421 (0) 2 571 04 501

Suomi/Finland

KRKA Finland Oy
Puh/Tel: +358 20 754 5330

Sverige

KRKA Sverige AB
Tel: + 46 (0)8 643 67 66 (SE)

United Kingdom

Consilient Health (UK) Ltd.
Tel: + 44 (0) 203 751 1888

This leaflet was last revised in

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

Package leaflet: Information for the user

Nimvastid 1.5 mg orodispersible tablets
Nimvastid 3 mg orodispersible tablets
Nimvastid 4.5 mg orodispersible tablets
Nimvastid 6 mg orodispersible tablets
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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. What Nimvastid is and what it is used for
2. What you need to know before you take Nimvastid
3. How to take Nimvastid
4. Possible side effects
5. How to store Nimvastid
6. Contents of the pack and other information

1. What Nimvastid is and what it is used for

The active substance of Nimvastid 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, Nimvastid 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.

Nimvastid 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 Nimvastid

Do not take Nimvastid

- if you are allergic to rivastigmine (the active substance in Nimvastid) or to any of the other ingredients of this medicine (listed in section 6).
- if you have a skin reaction spreading beyond the patch size, if there is a more intense local reaction (such as blisters, increasing skin inflammation, swelling) and if it does not improve within 48 hours after removal of the transdermal patch.

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

Warnings and precautions

Talk to your doctor before taking Nimvastid:

- if you have, or have ever had, irregular or slow heartbeat.
- if you have, or have ever had, an active stomach ulcer.
- if you have, or have ever had, difficulties in passing urine.
- if you have, or have ever had, seizures.
- if you have, or have ever had, asthma or severe respiratory disease.
- if you have, or have ever had impaired kidney function.
- if you have, or have ever had, impaired liver function.
- if you suffer from trembling.
- if you have a low body weight.
- if you have gastrointestinal reactions such as feeling sick (nausea), 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 Nimvastid 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 Nimvastid in the paediatric population in the treatment of Alzheimer's disease.

Other medicines and Nimvastid

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

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

Nimvastid 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 Nimvastid, tell your doctor before you are given any anaesthetics, because Nimvastid may exaggerate the effects of some muscle relaxants during anaesthesia.

Caution when Nimvastid 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.

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 Nimvastid must be assessed against the possible effects on your unborn child. Nimvastid should not be used during pregnancy unless clearly necessary.

You should not breast-feed during treatment with Nimvastid.

Driving and using machines

Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely. Nimvastid 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.

Nimvastid contains sorbitol E420

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take Nimvastid

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

How to start treatment

Your doctor will tell you what dose of Nimvastid 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.

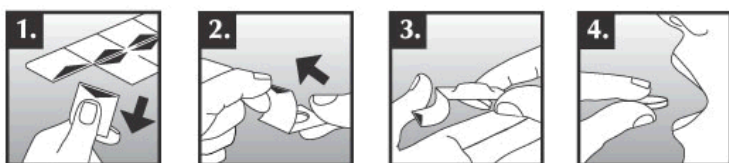
If you have not taken Nimvastid for more than three days, do not take the next dose until you have talked to your doctor.

Taking this medicine

- Tell your caregiver that you are taking Nimvastid.
- To benefit from your medicine, take it every day.
- Take Nimvastid twice a day, once with your breakfast and once with your evening meal. Your mouth should be empty before taking the tablet.

Nimvastid orodispersible tablets are fragile. They should not be pushed through the foil in the blister pack as this will cause damage to the tablet. Do not handle the tablets with wet hands as the tablets may break up. Remove a tablet from the package as follows:

1. Hold the blister at the edges and separate one blister cell from the rest of the blister by gently tearing along the perforations around it,
2. Pull up the edge of the foil and peel the foil off completely,
3. Tip the tablet out onto your hand.
4. Put the tablet on the tongue as soon as it is removed from the packaging.



In a few seconds it begins disintegrating in the mouth and subsequently can be swallowed without water. The mouth should be empty before placing the tablet on the tongue.

If you take more Nimvastid than you should

If you accidentally take more Nimvastid than you should, inform your doctor. You may require medical attention. Some people who have accidentally taken too much Nimvastid 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 Nimvastid

If you find you have forgotten to take your dose of Nimvastid, 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

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 rivastigmine transdermal patches and which may occur with the orodispersible tablets:

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, pharmacist or nurse. 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 Nimvastid

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

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

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. Contents of the pack and other information

What Nimvastid contains

- The active substance is rivastigmine hydrogen tartrate.
Each orodispersible tablet contains rivastigmine hydrogen tartrate equivalent to 1.5 mg, 3 mg, 4.5 mg or 6 mg rivastigmine.
- The other ingredients are mannitol, microcrystalline cellulose, hydroxypropylcellulose, spearmint flavour (peppermint oil, maize maltodextrin), peppermint flavour (maltodextrine, gum arabic, sorbitol E420, corn mint oil, L-menthol), crospovidone, calcium silicate, magnesium stearate.

What Nimvastid looks like and contents of the pack

Orodispersible tablets are round and white tablets.

14 x 1 (only for 1.5 mg), 28 x 1, 30 x 1, 56 x 1, 60 x 1 or 112 x 1 tablet in OPA/Alu/PVC foil film and PET/Alu peel off foil perforated unit dose blister packs are available.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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