ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Prometax 1.5 mg hard capsules
Prometax 3.0 mg hard capsules
Prometax 4.5 mg hard capsules
Prometax 6.0 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Prometax 1.5 mg hard capsules

Each capsule contains rivastigmine hydrogen tartrate corresponding to 1.5 mg rivastigmine.

Prometax 3.0 mg hard capsules

Each capsule contains rivastigmine hydrogen tartrate corresponding to 3.0 mg rivastigmine.

Prometax 4.5 mg hard capsules

Each capsule contains rivastigmine hydrogen tartrate corresponding to 4.5 mg rivastigmine.

Prometax 6.0 mg hard capsules

Each capsule contains rivastigmine hydrogen tartrate corresponding to 6.0 mg rivastigmine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

Prometax 1.5 mg hard capsules

Off-white to slightly yellow powder in a capsule with yellow cap and yellow body, with red imprint "ENA 713 1,5 mg" on body.

Prometax 3.0 mg hard capsules

Off-white to slightly yellow powder in a capsule with orange cap and orange body, with red imprint "ENA 713 3 mg" on body.

Prometax 4.5 mg hard capsules

Off-white to slightly yellow powder in a capsule with red cap and red body, with white imprint "ENA 713 4,5 mg" on body.

Prometax 6.0 mg hard capsules

Off-white to slightly yellow powder in a capsule with red cap and orange body, with red imprint "ENA 713 6 mg" on 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.

Special populations

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, Prometax 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 Prometax in the paediatric population in the treatment of Alzheimer's disease.

4.3 Contraindications

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, Prometax has been discontinued (see section 4.8).

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

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

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

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

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

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

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

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

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

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

Special populations

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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

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

Table 1

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

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

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

Table 2

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

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

Table 3 lists the number and percentage of patients from the specific 24-week clinical study conducted with Prometax 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	**Prometax n (%)**	**Placebo n (%)**
Total patients studied	362 (100)	179 (100)
Total patients with pre-defined AE(s)	99 (27.3)	28 (15.6)
Tremor	37 (10.2)	7 (3.9)
Fall	21 (5.8)	11 (6.1)
Parkinson's disease (worsening)	12 (3.3)	2 (1.1)
Salivary hypersecretion	5 (1.4)	0
Dyskinesia	5 (1.4)	1 (0.6)
Parkinsonism	8 (2.2)	1 (0.6)
Hypokinesia	1 (0.3)	0
Movement disorder	1 (0.3)	0
Bradykinesia	9 (2.5)	3 (1.7)
Dystonia	3 (0.8)	1 (0.6)
Gait abnormality	5 (1.4)	0
Muscle rigidity	1 (0.3)	0
Balance disorder	3 (0.8)	2 (1.1)
Musculoskeletal stiffness	3 (0.8)	0
Rigors	1 (0.3)	0
Motor dysfunction	1 (0.3)	0

Reporting of suspected adverse reactions

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

4.9 Overdose

Symptoms

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

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

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

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

Management

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, anticholinesterases, ATC code: N06DA03

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease and Parkinson's disease.

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

Clinical studies in Alzheimer's dementia

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

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

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

In addition, a post-hoc definition of response is provided in the same table. The secondary definition of response required a 4-point or greater improvement on the ADAS-Cog, no worsening on the CIBIC-Plus, and no worsening on the PDS. The mean actual daily dose for responders in the 6–12 mg group, corresponding to this definition, was 9.3 mg. It is important to note that the scales used in this indication vary and direct comparisons of results for different therapeutic agents are not valid.

Table 4

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

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

Clinical studies in dementia associated with Parkinson's disease

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

Table 5

Dementia associated with Parkinson's Disease	**ADAS-Cog Prometax**	**ADAS-Cog Placebo**	**ADCS-CGIC Prometax**	**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 Prometax**	**ADAS-Cog Placebo**	**ADAS-Cog Prometax**	**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 Prometax in all subsets of the paediatric population in the treatment of Alzheimer's dementia and in the treatment of dementia in patients with idiopathic Parkinson's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

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

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

Elimination

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

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

Special populations

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

Gelatin
Magnesium stearate
Hypromellose
Microcrystalline cellulose
Silica, colloidal anhydrous
Yellow iron oxide (E172)
Red iron oxide (E172)
Titanium dioxide (E171)
Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

Prometax 1.5 mg hard capsules

EU/1/98/092/001-3

Prometax 3.0 mg hard capsules

EU/1/98/092/004-6

Prometax 4.5 mg hard capsules

EU/1/98/092/007-9

Prometax 6.0 mg hard capsules

EU/1/98/092/010-12

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 December 1998
Date of latest renewal: 21 May 2008

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

Prometax 2 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect

Each 3 ml oral solution contains 3 mg of sodium benzoate (E211).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Clear, yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

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

Initial dose
1.5 mg twice a day.

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

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

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

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

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

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

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

Special populations

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, Prometax oral solution may be used in this patient population provided close monitoring is exercised (see sections 4.4 and 5.2).

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

4.3 Contraindications

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, Prometax has been discontinued (see section 4.8).

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

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

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

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

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

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

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

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

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

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

Special populations

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

Excipients with known effects

One of the excipients in Prometax oral solution is sodium benzoate (E211). Benzoic acid is a mild irritant to the skin, eyes and mucous membrane.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

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

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

Table 1

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

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

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

Table 2

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

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

Table 3 lists the number and percentage of patients from the specific 24-week clinical study conducted with Prometax 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	**Prometax 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.

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

Management

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psychoanaleptics, anticholinesterases, ATC code: N06DA03

Rivastigmine is an acetyl- and butyrylcholinesterase inhibitor of the carbamate type, thought to facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurones. Thus, rivastigmine may have an ameliorative effect on cholinergic-mediated cognitive deficits in dementia associated with Alzheimer's disease and Parkinson's disease.

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

Clinical studies in Alzheimer's dementia

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

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

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

In addition, a post-hoc definition of response is provided in the same table. The secondary definition of response required a 4-point or greater improvement on the ADAS-Cog, no worsening on the CIBIC-Plus, and no worsening on the PDS. The mean actual daily dose for responders in the 6–12 mg group, corresponding to this definition, was 9.3 mg. It is important to note that the scales used in this indication vary and direct comparisons of results for different therapeutic agents are not valid.

Table 4

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

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

Clinical studies in dementia associated with Parkinson's disease

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

Table 5

Dementia associated with Parkinson's Disease	**ADAS-Cog Prometax**	**ADAS-Cog Placebo**	**ADCS-CGIC Prometax**	**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 Prometax**	**ADAS-Cog Placebo**	**ADAS-Cog Prometax**	**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 Prometax in all subsets of the paediatric population in the treatment of Alzheimer's dementia and in the treatment of dementia in patients with idiopathic Parkinson's disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

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

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

Elimination

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

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

Special populations

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

Sodium benzoate (E211)
Citric acid
Sodium citrate
Quinoline yellow WS dye (E104)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Prometax oral solution should be used within 1 month of opening the bottle.

6.4 Special precautions for storage

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

Store in an upright position.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/013
EU/1/98/092/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 December 1998
Date of latest renewal: 21 May 2008

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

Prometax 4.6 mg/24 h transdermal patch
Prometax 9.5 mg/24 h transdermal patch
Prometax 13.3 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Prometax 4.6 mg/24 h transdermal patch

Each transdermal patch releases 4.6 mg of rivastigmine per 24 hours. Each transdermal patch of 5 cm^2 contains 9 mg of rivastigmine.

Prometax 9.5 mg/24 h transdermal patch

Each transdermal patch releases 9.5 mg of rivastigmine per 24 hours. Each transdermal patch of 10 cm^2 contains 18 mg of rivastigmine.

Prometax 13.3 mg/24 h transdermal patch

Each transdermal patch releases 13.3 mg of rivastigmine per 24 hours. Each transdermal patch of 15 cm^2 contains 27 mg of rivastigmine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch

Prometax 4.6 mg/24 h transdermal patch

Each transdermal patch is a thin, matrix-type transdermal patch consisting of three layers. The outside of the backing layer is beige and labelled with “Prometax”, “4.6 mg/24 h” and “AMCX”.

Prometax 9.5 mg/24 h transdermal patch

Each transdermal patch is a thin, matrix-type transdermal patch consisting of three layers. The outside of the backing layer is beige and labelled with “Prometax”, “9.5 mg/24 h” and “BHDI”.

Prometax 13.3 mg/24 h transdermal patch

Each transdermal patch is a thin, matrix-type transdermal patch consisting of three layers. The outside of the backing layer is beige and labelled with “Prometax”, “13.3 mg/24 h” and “CNFU”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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. Diagnosis should be made according to current guidelines. Similar to any treatment initiated in patients with dementia, therapy with rivastigmine should only be started if a caregiver is available to regularly administer and monitor the treatment.

Posology

Transdermal patches	**Rivastigmine *in vivo* release rates per 24 h**
Prometax 4.6 mg/24 h	4.6 mg
Prometax 9.5 mg/24 h	9.5 mg
Prometax 13.3 mg/24 h	13.3 mg

Initial dose
Treatment is started with 4.6 mg/24 h.

Maintenance dose
After a minimum of four weeks of treatment and if well tolerated according to the treating physician, the dose of 4.6 mg/24 h should be increased to 9.5 mg/24 h, the daily recommended effective dose, which should be continued for as long as the patient continues to demonstrate therapeutic benefit.

Dose escalation
9.5 mg/24 h is the recommended daily effective dose which should be continued for as long as the patient continues to demonstrate therapeutic benefit. If well tolerated and only after a minimum of six months of treatment at 9.5 mg/24 h, the treating physician may consider increasing the dose to 13.3 mg/24 h in patients who have demonstrated a meaningful cognitive deterioration (e.g. decrease in the MMSE) and/or functional decline (based on physician judgement) while on the recommended daily effective dose of 9.5 mg/24 h (see section 5.1).

The clinical benefit of rivastigmine should be reassessed on a regular basis. Discontinuation should also be considered when evidence of a therapeutic effect at the optimal dose is no longer present.

Treatment should be temporarily interrupted if gastrointestinal adverse reactions are observed until these adverse reactions resolve. Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than three days. Otherwise treatment should be re-initiated with 4.6 mg/24 h.

Switching from capsules or oral solution to transdermal patches
Based on comparable exposure between oral and transdermal rivastigmine (see section 5.2), patients treated with Prometax capsules or oral solution can be switched to Prometax transdermal patches as follows:

- A patient on a dose of 3 mg/day oral rivastigmine can be switched to 4.6 mg/24 h transdermal patches.
- A patient on a dose of 6 mg/day oral rivastigmine can be switched to 4.6 mg/24 h transdermal patches.
- A patient on a stable and well tolerated dose of 9 mg/day oral rivastigmine can be switched to 9.5 mg/24 h transdermal patches. If the oral dose of 9 mg/day has not been stable and well tolerated, a switch to 4.6 mg/24 h transdermal patches is recommended.
- A patient on a dose of 12 mg/day oral rivastigmine can be switched to 9.5 mg/24 h transdermal patches.

After switching to 4.6 mg/24 h transdermal patches, provided these are well tolerated after a minimum of four weeks of treatment, the dose of 4.6 mg/24 h should be increased to 9.5 mg/24 h, which is the recommended effective dose.

It is recommended to apply the first transdermal patch on the day following the last oral dose.

Special populations

- Paediatric population: There is no relevant use of Prometax in the paediatric population in the treatment of Alzheimer's disease.
- Patients with body weight below 50 kg: Particular caution should be exercised in titrating patients with body weight below 50 kg above the recommended effective dose of 9.5 mg/24 h (see section 4.4). They may experience more adverse reactions and may be more likely to discontinue due to adverse reactions.
- Hepatic impairment: Due to increased exposure in mild to moderate hepatic impairment as observed with the oral formulation, dosing recommendations to titrate according to individual tolerability should be closely followed. Patients with clinically significant hepatic impairment may experience more dose-dependent adverse reactions. Patients with severe hepatic impairment have not been studied. Particular caution should be exercised in titrating these patients (see sections 4.4 and 5.2).
- Renal impairment: No dose adjustment is necessary for patients with renal impairment (see section 5.2).

Method of administration

Transdermal patches should be applied once a day to clean, dry, hairless, intact healthy skin on the upper or lower back, upper arm or chest, in a place which will not be rubbed by tight clothing. It is not recommended to apply the transdermal patch to the thigh or to the abdomen due to decreased bioavailability of rivastigmine observed when the transdermal patch is applied to these areas of the body.

The transdermal patch should not be applied to skin that is red, irritated or cut. Reapplication to the exact same skin location within 14 days should be avoided to minimise the potential risk of skin irritation.

Patients and caregivers should be instructed on important administration instructions:

- The previous day's patch must be removed before applying a new one every day (see section 4.9).
- The patch should be replaced by a new one after 24 hours. Only one patch should be worn at a time (see section 4.9).
- The patch should be pressed down firmly for at least 30 seconds using the palm of the hand until the edges stick well.
- If the patch falls off, a new one should be applied for the rest of the day, then it should be replaced at the same time as usual the next day.
- The patch can be used in everyday situations, including bathing and during hot weather.
- The patch should not be exposed to any external heat sources (e.g. excessive sunlight, saunas, solarium) for long periods of time.
- The patch should not be cut into pieces.

4.3 Contraindications

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 increasing doses, particularly at dose changes. If treatment is interrupted for more than three days, it should be re-initiated with 4.6 mg/24 h.

Misuse of the medicinal product and dosing errors resulting in overdose

Misuse of the medicinal product and dosing errors with Prometax transdermal patch have resulted in serious adverse reactions; some cases have required hospitalisation, and rarely led to death (see section 4.9). Most cases of misuse of the medicinal product and dosing errors have involved not removing the old patch when putting on a new one and the use of multiple patches at the same time. Patients and their caregivers must be instructed on important administration instructions for Prometax transdermal patch (see section 4.2).

Gastrointestinal disorders

Gastrointestinal disorders such as nausea, vomiting and diarrhoea are dose-related, and may occur 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.

Weight loss

Patients with Alzheimer's disease may lose weight whilst taking cholinesterase inhibitors, including rivastigmine. The patient's weight should be monitored during therapy with Prometax transdermal patches.

Bradycardia

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

Other adverse reactions

Care must be taken when prescribing Prometax transdermal patches:

- to patients with sick sinus syndrome or conduction defects (sino-atrial block, atrio-ventricular block) (see section 4.8);
- to patients with active gastric or duodenal ulcers or patients predisposed to these conditions because rivastigmine may cause increased gastric secretions (see section 4.8);
- to patients predisposed to urinary obstruction and seizures because cholinomimetics may induce or exacerbate these diseases;
- to patients with a history of asthma or obstructive pulmonary disease.

Skin application site reactions

Skin application site reactions may occur with rivastigmine patch and are usually mild or moderate in intensity. Patients and caregivers should be instructed accordingly.

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).

Other warnings and precautions

Rivastigmine may exacerbate or induce extrapyramidal symptoms.

Contact with the eyes should be avoided after handling Prometax transdermal patches (see section 5.3). Hands should be washed with soap and water after removing the patch. In case of contact with eyes or if the eyes become red after handling the patch, rinse immediately with plenty of water and seek medical advice if symptoms do not resolve.

Special populations

- Patients with body weight below 50 kg may experience more adverse reactions and may be more likely to discontinue due to adverse reactions (see section 4.2). Carefully titrate and monitor these patients for adverse reactions (e.g. excessive nausea or vomiting) and consider reducing the maintenance dose to the 4.6 mg/24 h transdermal patch if such adverse reactions develop.
- Hepatic impairment: Patients with clinically significant hepatic impairment may experience more adverse reactions. Dosing recommendations to titrate according to individual tolerability must be closely followed. Patients with severe hepatic impairment have not been studied. Particular caution must be exercised in titrating these patients (see sections 4.2 and 5.2).

4.5 Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with Prometax transdermal patches.

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

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

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

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

No pharmacokinetic interaction was observed between oral 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 oral rivastigmine. No untoward effects on cardiac conduction were observed following concomitant administration of digoxin and oral rivastigmine.

Concomitant administration of rivastigmine with commonly prescribed medicinal products, such as antacids, antiemetics, antidiabetics, centrally acting antihypertensives, calcium channel blockers, inotropic agents, antianginals, non-steroidal anti-inflammatory agents, oestrogens, analgesics, benzodiazepines and antihistamines, was not associated with an alteration in the kinetics of rivastigmine or an increased risk of clinically relevant untoward effects.

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 machines. Furthermore, rivastigmine may induce syncope or delirium. As a consequence, rivastigmine has minor or moderate influence on the ability to drive and use machines. Therefore, in patients with dementia treated with rivastigmine, the ability to continue driving or operating complex machines should be routinely evaluated by the treating physician.

4.8 Undesirable effects

Summary of the safety profile

Application site skin reactions (usually mild to moderate application site erythema), are the most frequent adverse reactions observed with the use of Prometax transdermal patch. The next most common adverse reactions are gastrointestinal in nature including nausea and vomiting.

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

Tabulated list of adverse reactions

Table 1 displays the adverse reactions reported in 1,670 patients with Alzheimer's dementia treated in randomised, double-blind, placebo and active-controlled clinical studies with Prometax transdermal patches for a duration of 24-48 weeks and from post-marketing data.

Table 1

Infections and infestations	
Common	Urinary tract infection
Metabolism and nutrition disorders	
Common	Anorexia, decreased appetite
Uncommon	Dehydration
Psychiatric disorders	
Common	Anxiety, depression, delirium, agitation
Uncommon	Aggression
Not known	Hallucinations, restlessness, nightmares
Nervous system disorders	
Common	Headache, syncope, dizziness
Uncommon	Psychomotor hyperactivity
Very rare	Extrapyramidal symptoms
Not known	Worsening of Parkinson's disease, seizure, tremor, somnolence
Cardiac disorders	
Uncommon	Bradycardia
Not known	Atrioventricular block, atrial fibrillation, tachycardia, sick sinus syndrome
Vascular disorders	
Not known	Hypertension
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain
Uncommon	Gastric ulcer
Not known	Pancreatitis
Hepatobiliary disorders	
Not known	Hepatitis, elevated liver function tests
Skin and subcutaneous tissue disorders	
Common	Rash
Not known	Pruritus, erythema, urticaria, vesicles, allergic dermatitis (disseminated)
Renal and urinary disorders	
Common	Urinary incontinence
General disorders and administration site conditions	
Common	Application site skin reactions (e.g. application site erythema*, application site pruritus*, application site oedema*, application site dermatitis, application site irritation), asthenic conditions (e.g. fatigue, asthenia), pyrexia, weight decreased
Rare	Fall

*In a 24-week controlled study in Japanese patients, application site erythema, application site oedema and application site pruritus were reported as "very common".

Description of selected adverse reactions

When doses higher than 13.3 mg/24 h were used in the above-mentioned placebo-controlled study, insomnia and cardiac failure were observed more frequently than with 13.3 mg/24 h or placebo, suggesting a dose effect relationship. However, these events did not occur at a higher frequency with Prometax 13.3 mg/24 h transdermal patches than with placebo.

The following adverse reactions have only been observed with Prometax capsules and oral solution and not in clinical studies with Prometax transdermal patches: malaise, confusion, sweating increased (common); duodenal ulcers, angina pectoris (rare); gastrointestinal haemorrhage (very rare); and some cases of severe vomiting were associated with oesophageal rupture (not known).

Skin irritation
In double-blind controlled clinical trials, application site reactions were mostly mild to moderate in severity. The incidence of application site skin reactions leading to discontinuation was ≤2.3% in patients treated with Prometax transdermal patches. The incidence of application site skin reactions leading to discontinuation was higher in the Asian population with 4.9% and 8.4% in the Chinese and Japanese population respectively.

In two 24-week double-blind, placebo-controlled clinical trials, skin reactions were measured at each visit using a skin irritation rating scale. When observed in patients treated with Prometax transdermal patches, skin irritation was mostly slight or mild in severity. It was rated as severe in ≤2.2% of patients in these studies and in ≤3.7% of patients treated with Prometax transdermal patches in a Japanese study.

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 of oral rivastigmine 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.

Additionaly there have been post-marketing cases of dizziness, tremor, headache, somnolence, confusional state, hypertension, hallucinations and malaise. Overdose with Prometax transdermal patch resulting from misuse/dosing errors (application of multiple patches at a time) has been reported in the post-marketing setting and rarely in clinical trials.

Management

As rivastigmine has a plasma half-life of about 3.4 hours and a duration of acetylcholinesterase inhibition of about 9 hours, it is recommended that in cases of asymptomatic overdose all Prometax transdermal patches should be removed immediately and no further transdermal patch should be applied 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.

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 oral 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 oral rivastigmine was similar to the inhibition of AChE activity.

Clinical studies in Alzheimer's dementia

The efficacy of Prometax transdermal patches in patients with Alzheimer's dementia has been demonstrated in a 24-week double-blind, placebo-controlled core study and its open-label extension phase and in a 48-week double-blind comparator study.

24-week placebo-controlled study
Patients involved in the placebo-controlled study had an MMSE (Mini-Mental State Examination) score of 10–20. Efficacy was established by the use of independent, domain-specific assessment tools which were applied at regular intervals during the 24-week treatment period. These include the ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale, a performance-based measure of cognition) and the ADCS-CGIC (Alzheimer's Disease Cooperative Study – Clinician's Global Impression of Change, a comprehensive global assessment of the patient by the physician incorporating caregiver input), and the ADCS-ADL (Alzheimer's Disease Cooperative Study – Activities of Daily Living, 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 related to finances). The 24-week results for the three assessment tools are summarised in Table 2.

Table 2

ITT-LOCF population	Prometax transdermal patches 9.5 mg/24 h N = 251	Prometax capsules 12 mg/day N = 256	Placebo N = 282
ADAS-Cog			
	(n=248)	(n=253)	(n=281)
Mean baseline ± SD	27.0 ± 10.3	27.9 ± 9.4	28.6 ± 9.9
Mean change at week 24 ± SD	-0.6 ± 6.4	-0.6 ± 6.2	1.0 ± 6.8
p-value versus placebo	0.005*[1]	0.003*[1]	
ADCS-CGIC			
	(n=248)	(n=253)	(n=278)
Mean score ± SD	3.9 ± 1.20	3.9 ± 1.25	4.2 ± 1.26
p-value versus placebo	0.010*[2]	0.009*[2]	
ADCS-ADL			
	(n=247)	(n=254)	(n=281)
Mean baseline ± SD	50.1 ± 16.3	49.3 ± 15.8	49.2 ± 16.0
Mean change at week 24 ± SD	-0.1 ± 9.1	-0.5 ± 9.5	-2.3 ± 9.4
p-value versus placebo	0.013*[1]	0.039*[1]	

* p≤0.05 versus placebo
ITT: Intent-To-Treat; LOCF: Last Observation Carried Forward
[1] Based on ANCOVA with treatment and country as factors and baseline value as a covariate. Negative ADAS-Cog changes indicate improvement. Positive ADCS-ADL changes indicate improvement.
[2] Based on CMH test (van Elteren test) blocking for country. ADCS-CGIC scores <4 indicate improvement.

The results for clinically relevant responders from the 24-week placebo-controlled study are provided in Table 3. Clinically relevant improvement was defined a priori as at least 4-point improvement on the ADAS-Cog, no worsening on the ADCS-CGIC, and no worsening on the ADCS-ADL.

Table 3

	Patients with clinically significant response (%)		
ITT-LOCF population	Prometax transdermal patches 9.5 mg/24 h N = 251	Prometax capsules 12 mg/day N = 256	Placebo N = 282
At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL	17.4	19.0	10.5
p-value versus placebo	0.037*	0.004*	

*p<0.05 versus placebo

As suggested by compartmental modelling, 9.5 mg/24 h transdermal patches exhibited exposure similar to that provided by an oral dose of 12 mg/day.

48-week active comparator controlled study

Patients involved in the active comparator controlled study had an initial baseline MMSE score of 10-24. The study was designed to compare the efficacy of the 13.3 mg/24 h transdermal patch against the 9.5 mg/24 h transdermal patch during a 48-week double-blind treatment phase in Alzheimer's disease patients who demonstrated functional and cognitive decline after an initial 24-48 week open-label treatment phase while on a maintenance dose of 9.5 mg/24 h transdermal patch. Functional decline was assessed by the investigator and cognitive decline was defined as a decrease in the MMSE score of ≥2 points from the previous visit or a decrease of ≥3 points from baseline. Efficacy was established by the use of ADAS-Cog (Alzheimer's Disease Assessment Scale – Cognitive subscale, a performance-based measure of cognition) and the ADCS-IADL (Alzheimer's Disease Cooperative Study – Instrumental Activities of Daily Living) assessing instrumental activities which include maintaining finances, meal preparation, shopping, ability to orient oneself to surroundings, ability to be left unattended. The 48-week results for the two assessment tools are summarised in Table 4.

Table 4

Population/Visit			**Prometax 15 cm^2 N = 265**		**Prometax 10 cm^2 N = 271**		**Prometax 15 cm^2**		**Prometax 10 cm^2**
			n	**Mean**	**n**	**Mean**	**DLSM**	**95% CI**	**p-value**
ADAS-Cog									
LOCF		Baseline	264	34.4	268	34.9			
	DB-week 48	Value	264	38.5	268	39.7			
		Change	264	4.1	268	4.9	-0.8	(-2.1, 0.5)	0.227
ADCS-IADL									
LOCF		Baseline	265	27.5	271	25.8			
	Week 48	Value	265	23.1	271	19.6			
		Change	265	-4.4	271	-6.2	2.2	(0.8, 3.6)	0.002*

CI – confidence interval.
DLSM – difference in least square means.
LOCF – Last Observation Carried Forward.
ADAS-cog scores: A negative difference in DLSM indicates greater improvement in Prometax 15 cm^2 as compared to Prometax 10 cm^2.
ADCS-IADL scores: A positive difference in DLSM indicates greater improvement in Prometax 15 cm^2 as compared to Prometax 10 cm^2.
N is the number of patients with an assessment at baseline (last assessment in the initial open-label phase) and with at least 1 post-baseline assessment (for the LOCF).
The DLSM, 95% CI, and p-value are based on an ANCOVA (analysis of covariance) model adjusted for country and baseline ADAS-cog score.
* $p<0.05$
Source: Study D2340-Table 11-6 and Table 11-7

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

5.2 Pharmacokinetic properties

Absorption

Absorption of rivastigmine from Prometax transdermal patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5-1 hour. C_{max} is reached after 10-16 hours. After the peak, plasma concentrations slowly decrease over the remainder of the 24-hour period of application. With multiple dosing (such as at steady state), after the previous transdermal patch is replaced with a new one, plasma concentrations initially decrease slowly for about 40 minutes on average, until absorption from the newly applied transdermal patch becomes faster than elimination, and plasma levels begin to rise again to reach a new peak at approximately 8 hours. At steady state, trough levels are approximately 50% of peak levels, in contrast to oral administration, with which concentrations fall off to virtually zero between doses. Although less pronounced than with the oral formulation, exposure to rivastigmine (C_{max} and AUC) increased over-proportionally by a factor of 2.6 and 4.9 when escalating from 4.6 mg/24 h to 9.5 mg/24 h and to 13.3 mg/24 h, respectively. The fluctuation index (FI), a measure of the relative difference between peak and trough concentrations ($(C_{max}-C_{min})/C_{avg}$), was 0.58 for Prometax 4.6 mg/24 h transdermal patches, 0.77 for Prometax 9.5 mg/24 h transdermal patches and 0.72 for Prometax 13.3 mg/24 h transdermal patches, thus demonstrating a much smaller fluctuation between trough and peak concentrations than for the oral formulation (FI = 3.96 (6 mg/day) and 4.15 (12 mg/day)).

The dose of rivastigmine released from the transdermal patch over 24 hours (mg/24 h) cannot be directly equated to the amount (mg) of rivastigmine contained in a capsule with respect to plasma concentration produced over 24 hours.

The single-dose inter-subject variability in rivastigmine pharmacokinetic parameters (normalised to dose/kg bodyweight) was 43% (C_{max}) and 49% (AUC_{0-24h}) after transdermal administration versus 74% and 103%, respectively, after the oral form. The inter-patient variability in a steady-state study in Alzheimer's dementia was at most 45% (C_{max}) and 43% (AUC_{0-24h}) after use of the transdermal patch, and 71% and 73%, respectively, after administration of the oral form.

A relationship between active substance exposure at steady state (rivastigmine and metabolite NAP226-90) and bodyweight was observed in Alzheimer's dementia patients. Compared to a patient with a body weight of 65 kg, the rivastigmine steady-state concentrations in a patient with a body weight of 35 kg would be approximately doubled, while for a patient with a body weight of 100 kg the concentrations would be approximately halved. The effect of bodyweight on active substance exposure suggests special attention to patients with very low body weight during up-titration (see section 4.4).

Exposure (AUC_{∞}) to rivastigmine (and metabolite NAP266-90) was highest when the transdermal patch was applied to the upper back, chest, or upper arm and approximately 20–30% lower when applied to the abdomen or thigh.

There was no relevant accumulation of rivastigmine or the metabolite NAP226-90 in plasma in patients with Alzheimer's disease, except that plasma levels were higher on the second day of transdermal patch therapy than on the first.

Distribution

Rivastigmine is weakly bound to plasma proteins (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 with an apparent elimination half-life in plasma of approximately 3.4 hours after removal of the transdermal patch. Elimination was absorption rate limited (flip-flop kinetics), which explains the longer $t_{½}$ after transdermal patch (3.4 h) versus oral or intravenous administrations (1.4 to 1.7 h). Metabolism is primarily via cholinesterase-mediated hydrolysis to the metabolite NAP226-90. *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 cytochrome 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 litres/h after a 0.2 mg intravenous dose and decreased to 70 litres/h after a 2.7 mg intravenous dose, which is consistent with the non-linear, over-proportional pharmacokinetics of rivastigmine due to saturation of its elimination.

The metabolite-to-parent AUC_{∞} ratio was around 0.7 after transdermal patch administration versus 3.5 after oral administration, indicating that much less metabolism occurred after dermal compared to oral treatment. Less NAP226-90 is formed following application of the transdermal patch, presumably because of the lack of presystemic (hepatic first pass) metabolism, in contrast to oral administration.

Elimination

Unchanged rivastigmine is found in trace amounts in the urine; renal excretion of the metabolites is the major route of elimination after transdermal patch administration. Following administration of oral ^{14}C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces.

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 for up to 12 mg/day.

Special populations

Elderly
Age had no impact on the exposure to rivastigmine in Alzheimer's disease patients treated with Prometax transdermal patches.

Hepatic impairment
No study was conducted with Prometax transdermal patches in subjects with hepatic impairment. After oral administration, 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.

Following a single 3 mg or 6 mg oral dose, the mean oral clearance of rivastigmine was approximately 46-63% lower in patients with mild to moderate hepatic impairment (n=10, Child-Pugh score 5-12, biopsy proven) than in healthy subjects (n=10).

Renal impairment
No study was conducted with Prometax transdermal patches in subjects with renal impairment. Based on population analysis, creatinine clearance did not show any clear effect on steady state concentrations of rivastigmine or its metabolite. No dose adjustment is necessary in patients with renal impairment (see section 4.2).

5.3 Preclinical safety data

Oral and topical repeated-dose toxicity studies in mice, rats, rabbits, dogs and minipigs revealed only effects associated with an exaggerated pharmacological action. No target organ toxicity was observed. Oral and topical dosing in animal studies was limited 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 exceeding 10^4 times the foreseen 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 oral and topical studies in mice and in an oral study in rats at the maximum tolerated dose. The exposure to rivastigmine and its metabolites was approximately equivalent to human exposure with highest doses of rivastigmine capsules and transdermal patches.

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. Specific dermal studies in pregnant animals have not been conducted.

Rivastigmine transdermal patches were not phototoxic and considered to be a non-sensitiser. In some other dermal toxicity studies, a mild irritant effect on the skin of laboratory animals, including controls, was observed. This may indicate a potential for Prometax transdermal patches to induce mild erythema in patients.

A mild eye/mucosal irritation potential of rivastigmine was identified in a rabbit study. Therefore, the patient/caregiver should avoid contact with the eyes after handling of the patch (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Backing layer

Polyethylene terephthalate film, lacquered

Medicinal product matrix

Alpha-tocopherol
Poly(butylmethacrylate, methylmethacrylate)
Acrylic copolymer

Adhesive matrix

Alpha-tocopherol
Silicone oil
Dimethicone

Release liner

Polyester film, fluoropolymer-coated

6.2 Incompatibilities

To prevent interference with the adhesive properties of the transdermal patch, no cream, lotion or powder should be applied to the skin area where the medicinal product is to be applied.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.
Keep the transdermal patch in the sachet until use.

6.5 Nature and contents of container

Prometax 9 mg/5 cm^2, 18 mg/10 cm^2 and 27 mg/15 cm^2 transdermal patches are individually packaged in child-resistant, heat-sealed sachets made of a paper/polyethyleneterephthalate/aluminum/polyacrylnitrile (PAN) multi-laminated material (paper/PET/alu/PAN) or in heat-sealed, child-resistant sachets made of multi-layer composite laminate consisting of paper/polyethylene terephthalate/polyethylene/aluminum/polyamide (paper/PET/PE/alu/PA).

Available in packs containing 7 or 30 sachets and in multipacks containing 60 or 90 sachets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Used transdermal patches should be folded in half, with the adhesive side inwards, placed in the original sachet and discarded safely and out of the reach and sight of children. Any used or unused transdermal patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBERS

Prometax 4.6 mg/24 h transdermal patch

EU/1/98/092/019-022
EU/1/98/092/031-034

Prometax 9.5 mg/24 h transdermal patch

EU/1/98/092/023-026
EU/1/98/092/035-038

Prometax 13.3 mg/24 h transdermal patch

EU/1/98/092/027-030
EU/1/98/092/039-042

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 December 1998
Date of latest renewal: 21 May 2008

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. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

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

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

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

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

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

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

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

- **Risk management plan (RMP)**

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

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

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Prometax patch is marketed, all physicians who are expected to prescribe Prometax patch are provided with an information pack containing the following elements:
- The Summary of Product Characteristics
- Patient reminder card
- Instructions to provide patients and caregivers with the patient reminder card

The patient reminder card should contain the following key messages:
- Take off the previous patch before putting ONE new patch on.
- Only one patch per day.
- Do not cut the patch into pieces.
- Press the patch firmly in place for at least 30 seconds using the palm of the hand.
- How to use the reminder card to record patch application and removal.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Prometax 1.5 mg hard capsules
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains 1.5 mg rivastigmine present as rivastigmine hydrogen tartrate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/001	28 hard capsules
EU/1/98/092/002	56 hard capsules
EU/1/98/092/003	112 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 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

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Prometax 1.5 mg hard capsules
rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Prometax 3.0 mg hard capsules
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains 3.0 mg rivastigmine present as rivastigmine hydrogen tartrate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/004	28 hard capsules
EU/1/98/092/005	56 hard capsules
EU/1/98/092/006	112 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 3.0 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

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Prometax 3.0 mg hard capsules
rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Prometax 4.5 mg hard capsules
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains 4.5 mg rivastigmine present as rivastigmine hydrogen tartrate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/007	28 hard capsules
EU/1/98/092/008	56 hard capsules
EU/1/98/092/009	112 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 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

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Prometax 4.5 mg hard capsules
rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Prometax 6.0 mg hard capsules
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 capsule contains 6.0 mg rivastigmine present as rivastigmine hydrogen tartrate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard capsules
56 hard capsules
112 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Do not store above 30°C.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/010	28 hard capsules
EU/1/98/092/011	56 hard capsules
EU/1/98/092/012	112 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 6.0 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

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Prometax 6.0 mg hard capsules
rivastigmine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

FOLDING BOX AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Prometax 2 mg/ml oral solution
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 2 mg rivastigmine present as rivastigmine hydrogen tartrate.

3. LIST OF EXCIPIENTS

Also contains: sodium benzoate (E211), citric acid, sodium citrate, quinoline yellow dye (E104) and purified water.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

50 ml
120 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use Prometax oral solution within 1 month of opening the bottle.

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/018 50 ml
EU/1/98/092/013 120 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 2 mg/ml [folding box only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included. [folding box only]

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC [folding box only]
SN [folding box only]
NN [folding box only]

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Prometax 4.6 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 5 cm^2 contains 9 mg rivastigmine and delivers 4.6 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains: polyethylene terephthalate film lacquered, alpha-tocopherol, poly(butylmethacrylate, methylmethacrylate), acrylic copolymer, silicone oil, dimethicone, polyester film fluoropolymer-coated.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
30 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the patch in the sachet until use.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/019	7 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/020	30 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/031	7 transdermal patches (sachet: paper/PET/PE/alu/PA)
EU/1/98/092/032	30 transdermal patches (sachet: paper/PET/PE/alu/PA)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 4.6 mg/24 h

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Prometax 4.6 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 5 cm^2 contains 9 mg rivastigmine and delivers 4.6 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains: polyethylene terephthalate film lacquered, alpha-tocopherol, poly(butylmethacrylate, methylmethacrylate), acrylic copolymer, silicone oil, dimethicone, polyester film fluoropolymer-coated.

4. PHARMACEUTICAL FORM AND CONTENTS

30 transdermal patches. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the patch in the sachet until use.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/021	60 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/022	90 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/033	60 transdermal patches (sachet: paper/PET/PE/alu/PA)
EU/1/98/092/034	90 transdermal patches (sachet: paper/PET/PE/alu/PA)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 4.6 mg/24 h

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Prometax 4.6 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 5 cm^2 contains 9 mg rivastigmine and delivers 4.6 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains: polyethylene terephthalate film lacquered, alpha-tocopherol, poly(butylmethacrylate, methylmethacrylate), acrylic copolymer, silicone oil, dimethicone, polyester film fluoropolymer-coated.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 60 (2 packs of 30) transdermal patches
Multipack: 90 (3 packs of 30) transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the patch in the sachet until use.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/021	60 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/022	90 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/033	60 transdermal patches (sachet: paper/PET/PE/alu/PA)
EU/1/98/092/034	90 transdermal patches (sachet: paper/PET/PE/alu/PA)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 4.6 mg/24 h

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 SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prometax 4.6 mg/24 h transdermal patch
rivastigmine

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch per sachet

6. OTHER

Apply one patch per day. Take off the previous patch before putting ONE new patch on.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Prometax 9.5 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 10 cm^2 contains 18 mg rivastigmine and delivers 9.5 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains: polyethylene terephthalate film lacquered, alpha-tocopherol, poly(butylmethacrylate, methylmethacrylate), acrylic copolymer, silicone oil, dimethicone, polyester film fluoropolymer-coated.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
30 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the patch in the sachet until use.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/023	7 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/024	30 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/035	7 transdermal patches (sachet: paper/PET/PE/alu/PA)
EU/1/98/092/036	30 transdermal patches (sachet: paper/PET/PE/alu/PA)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 9.5 mg/24 h

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Prometax 9.5 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 10 cm^2 contains 18 mg rivastigmine and delivers 9.5 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains: polyethylene terephthalate film lacquered, alpha-tocopherol, poly(butylmethacrylate, methylmethacrylate), acrylic copolymer, silicone oil, dimethicone, polyester film fluoropolymer-coated.

4. PHARMACEUTICAL FORM AND CONTENTS

30 transdermal patches. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the patch in the sachet until use.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/025	60 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/026	90 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/037	60 transdermal patches (sachet: paper/PET/PE/alu/PA)
EU/1/98/092/038	90 transdermal patches (sachet: paper/PET/PE/alu/PA)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 9.5 mg/24 h

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Prometax 9.5 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 10 cm^2 contains 18 mg rivastigmine and delivers 9.5 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains: polyethylene terephthalate film lacquered, alpha-tocopherol, poly(butylmethacrylate, methylmethacrylate), acrylic copolymer, silicone oil, dimethicone, polyester film fluoropolymer-coated.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 60 (2 packs of 30) transdermal patches
Multipack: 90 (3 packs of 30) transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the patch in the sachet until use.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/025	60 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/026	90 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/037	60 transdermal patches (sachet: paper/PET/PE/alu/PA)
EU/1/98/092/038	90 transdermal patches (sachet: paper/PET/PE/alu/PA)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 9.5 mg/24 h

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 SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prometax 9.5 mg/24 h transdermal patch
rivastigmine

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch per sachet

6. OTHER

Apply one patch per day. Take off the previous patch before putting ONE new patch on.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Prometax 13.3 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 15 cm^2 contains 27 mg rivastigmine and delivers 13.3 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains: polyethylene terephthalate film lacquered, alpha-tocopherol, poly(butylmethacrylate, methylmethacrylate), acrylic copolymer, silicone oil, dimethicone, polyester film fluoropolymer-coated.

4. PHARMACEUTICAL FORM AND CONTENTS

7 transdermal patches
30 transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the patch in the sachet until use.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/027	7 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/028	30 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/039	7 transdermal patches (sachet: paper/PET/PE/alu/PA)
EU/1/98/092/040	30 transdermal patches (sachet: paper/PET/PE/alu/PA)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 13.3 mg/24 h

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Prometax 13.3 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 15 cm^2 contains 27 mg rivastigmine and delivers 13.3 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains: polyethylene terephthalate film lacquered, alpha-tocopherol, poly(butylmethacrylate, methylmethacrylate), acrylic copolymer, silicone oil, dimethicone, polyester film fluoropolymer-coated.

4. PHARMACEUTICAL FORM AND CONTENTS

30 transdermal patches. Component of a multipack. Not to be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the patch in the sachet until use.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/029	60 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/030	90 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/041	60 transdermal patches (sachet: paper/PET/PE/alu/PA)
EU/1/98/092/042	90 transdermal patches (sachet: paper/PET/PE/alu/PA)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 13.3 mg/24 h

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Prometax 13.3 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 15 cm^2 contains 27 mg rivastigmine and delivers 13.3 mg/24 h.

3. LIST OF EXCIPIENTS

Also contains: polyethylene terephthalate film lacquered, alpha-tocopherol, poly(butylmethacrylate, methylmethacrylate), acrylic copolymer, silicone oil, dimethicone, polyester film fluoropolymer-coated.

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack: 60 (2 packs of 30) transdermal patches
Multipack: 90 (3 packs of 30) transdermal patches

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the patch in the sachet until use.

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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/092/029	60 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/030	90 transdermal patches (sachet: paper/PET/alu/PAN)
EU/1/98/092/041	60 transdermal patches (sachet: paper/PET/PE/alu/PA)
EU/1/98/092/042	90 transdermal patches (sachet: paper/PET/PE/alu/PA)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Prometax 13.3 mg/24 h

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 SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Prometax 13.3 mg/24 h transdermal patch
rivastigmine

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Transdermal use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 transdermal patch per sachet

6. OTHER

Apply one patch per day. Take off the previous patch before putting ONE new patch on.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Prometax 1.5 mg hard capsules
Prometax 3.0 mg hard capsules
Prometax 4.5 mg hard capsules
Prometax 6.0 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, pharmacist or nurse.
- 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 Prometax is and what it is used for

The active substance of Prometax 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, Prometax 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.

Prometax 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 Prometax

Do not take Prometax
- if you are allergic to rivastigmine (the active substance in Prometax) or 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 Prometax.

Warnings and precautions
Talk to your doctor before taking Prometax:
- if you have, or have ever had, a heart condition such as an irregular or slow heartbeat, QTc prolongation, a family history of QTc prolongation, torsade de pointes, or have a low blood level of potassium or magnesium.
- if you have, or have ever had, an active stomach ulcer.
- if you have, or have ever had, difficulties in passing urine.
- if you have, or have ever had, seizures.
- if you have, or have ever had, asthma or severe respiratory disease.
- if you have, or have ever had impaired kidney function.
- if you have, or have ever had, impaired liver function.
- if you suffer from trembling.
- if you have a low body weight.
- if you have gastrointestinal reactions such as feeling sick (nausea), being sick (vomiting) and diarrhoea. You may become dehydrated (losing too much fluid) if vomiting or diarrhoea are prolonged.

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

If you have not taken Prometax 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 Prometax in the paediatric population in the treatment of Alzheimer's disease.

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

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

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

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

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

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

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

You should not breast-feed during treatment with Prometax.

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

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 Prometax 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 Prometax 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 Prometax.
- To benefit from your medicine, take it every day.
- Take Prometax 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 Prometax than you should
If you accidentally take more Prometax than you should, inform your doctor. You may require medical attention. Some people who have accidentally taken too much Prometax 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 Prometax
If you find you have forgotten to take your dose of Prometax, 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 Prometax 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 Prometax

- 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 carton after EXP. The expiry date refers to the last day of that month.
- Do not store above 30°C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Prometax contains
- The active substance is rivastigmine hydrogen tartrate.
- The other ingredients are hypromellose, magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica, gelatin, yellow iron oxide (E172), red iron oxide (E172), titanium dioxide (E171) and shellac.

Each Prometax 1.5 mg capsule contains 1.5 mg of rivastigmine.
Each Prometax 3.0 mg capsule contains 3.0 mg of rivastigmine.
Each Prometax 4.5 mg capsule contains 4.5 mg of rivastigmine.
Each Prometax 6.0 mg capsule contains 6.0 mg of rivastigmine.

What Prometax looks like and contents of the pack
- Prometax 1.5 mg hard capsules, which contain an off-white to slightly yellow powder, have a yellow cap and yellow body, with red imprint “ENA 713 1,5 mg” on the body.
- Prometax 3.0 mg hard capsules, which contain an off-white to slightly yellow powder, have an orange cap and orange body, with a red imprint “ENA 713 3 mg” on the body.
- Prometax 4.5 mg hard capsules, which contain an off-white to slightly yellow powder, have a red cap and red body, with a white imprint “ENA 713 4,5 mg” on the body.
- Prometax 6.0 mg hard capsules, which contain an off-white to slightly yellow powder, have a red cap and orange body, with a red imprint “ENA 713 6 mg” on the body.

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

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

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

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

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

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma GmbH
Tél/Tel: +49 911 273 0

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Sandoz Polska Sp. z o.o.
Tel.: +48 22 549 1500

Portugal
Laboratório Normal - Produtos Farmacêuticos, Lda.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom (Northern Ireland)
Novartis Ireland Limited
Tel: +44 1276 698370

This leaflet was last revised in

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

Package leaflet: Information for the user

Prometax 2 mg/ml oral solution
rivastigmine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- 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 Prometax is and what it is used for

The active substance of Prometax 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, Prometax 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.

Prometax 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 Prometax

Do not take Prometax
- if you are allergic to rivastigmine (the active substance in Prometax) or 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 Prometax.

Warnings and precautions
Talk to your doctor before taking Prometax:
- if you have, or have ever had, a heart condition such as an irregular or slow heartbeat, QTc prolongation, a family history of QTc prolongation, torsade de pointes, or have a low blood level of potassium or magnesium.
- if you have, or have ever had, an active stomach ulcer.
- if you have, or have ever had, difficulties in passing urine.
- if you have, or have ever had, seizures.
- if you have, or have ever had, asthma or severe respiratory disease.
- if you have, or have ever had impaired kidney function.
- if you have, or have ever had, impaired liver function.
- if you suffer from trembling.
- if you have a low body weight.
- if you have gastrointestinal reactions such as feeling sick (nausea), being sick (vomiting) and diarrhoea. You may become dehydrated (losing too much fluid) if vomiting or diarrhoea are prolonged.

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

If you have not taken Prometax 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 Prometax in the paediatric population in the treatment of Alzheimer's disease.

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

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

Prometax 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 such as stiff limbs and trembling hands.

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

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

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

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

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

You should not breast-feed during treatment with Prometax.

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

Prometax contains sodium benzoate (E211) and sodium
One of the inactive ingredients in Prometax oral solution is sodium benzoate (E211). Benzoic acid is a mild irritant to the skin, eyes and mucous membranes. This medicine contains 3 mg of sodium benzoate (E211) in each 3 ml of oral solution.

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

3. How to take Prometax

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

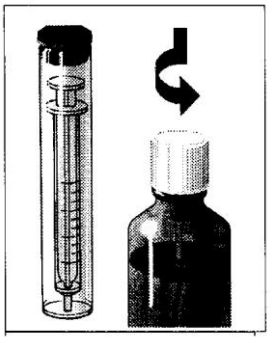
How to start treatment
Your doctor will tell you what dose of Prometax to take.
- Treatment usually starts with a low dose.
- Your doctor will slowly increase your dose depending on how you respond to the treatment.
- The highest dose that should be taken is 6.0 mg twice a day.

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

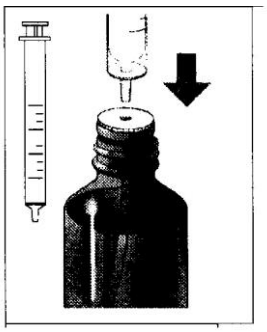
If you have not taken Prometax for more than three days, do not take the next dose until you have talked to your doctor.

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

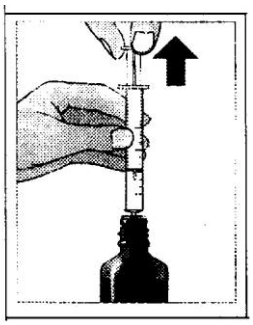
How to use this medicine



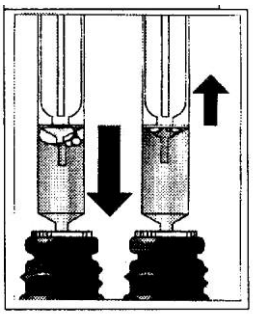
1. Preparing the bottle and syringe
   - Take the syringe out of its protective case.
   - Push down and turn the child resistant cap to open bottle.



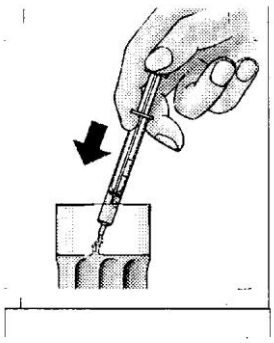
2. Attaching the syringe to the bottle
   - Push the nozzle of the syringe into the hole in the white stopper.



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



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



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

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

If you take more Prometax than you should
If you accidentally take more Prometax than you should, inform your doctor. You may require medical attention. Some people who have accidentally taken too much Prometax 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 Prometax
If you find you have forgotten to take your dose of Prometax, 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 Prometax transdermal patches and which may occur with the oral solution:

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

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

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

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

Reporting of side effects
If you get any side effects, talk to your doctor, 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 Prometax

- 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 carton after EXP. The expiry date refers to the last day of that month.
- Do not store above 30°C. Do not refrigerate or freeze.
- Store in an upright position.
- Use Prometax oral solution within 1 month of opening the bottle.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Prometax contains
- The active substance is rivastigmine hydrogen tartrate. Each ml contains rivastigmine hydrogen tartrate corresponding to rivastigmine base 2.0 mg.
- The other ingredients are sodium benzoate (E211), citric acid, sodium citrate, quinoline yellow WS dye (E104) and purified water.

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

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

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

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

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

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma GmbH
Tél/Tel: +49 911 273 0

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 88 04 52 111

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Laboratório Normal - Produtos Farmacêuticos, Lda.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom (Northern Ireland)
Novartis Ireland Limited
Tel: +44 1276 698370

This leaflet was last revised in

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

Package leaflet: Information for the user

Prometax 4.6 mg/24 h transdermal patch
Prometax 9.5 mg/24 h transdermal patch
Prometax 13.3 mg/24 h transdermal patch
rivastigmine

Read all of this leaflet carefully before you start using 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, pharmacist or nurse.
- 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 Prometax is and what it is used for

The active substance of Prometax is rivastigmine.

Rivastigmine belongs to a class of substances called cholinesterase inhibitors. In patients with Alzheimer's dementia, 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, Prometax allows levels of acetylcholine to be increased in the brain, helping to reduce the symptoms of Alzheimer's disease.

Prometax 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.

2. What you need to know before you use Prometax

Do not use Prometax
- if you are allergic to rivastigmine (the active substance in Prometax) or any of the other ingredients of this medicine (listed in section 6).
- if you have ever had an allergic reaction to a similar type of medicine (carbamate derivatives).
- 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 apply Prometax transdermal patches.

Warnings and precautions
Talk to your doctor before using Prometax:
- if you have, or have ever had, a heart condition such as an irregular or slow heartbeat, QTc prolongation, a family history of QTc prolongation, torsade de pointes, or have a low blood level of potassium or magnesium.
- if you have, or have ever had, an active stomach ulcer.
- if you have, or have ever had, difficulties in passing urine.
- if you have, or have ever had, seizures.
- if you have, or have ever had, asthma or a severe respiratory disease.
- 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 you have impaired liver function.

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 applied a patch for more than three days, do not apply the next one before you have talked to your doctor.

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

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

Prometax might interfere with anticholinergic medicines some of which are medicines used to relieve stomach cramps or spasms (e.g. dicyclomine), to treat Parkinson's disease (e.g. amantadine) or to prevent motion sickness (e.g. diphenhydramine, scopolamine, or meclizine).

Prometax Patch 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 using Prometax transdermal patches, tell your doctor that you are using them because they may exaggerate the effects of some muscle relaxants during anaesthesia.

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

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

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

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

You should not breast-feed during treatment with Prometax transdermal patches.

Driving and using machines
Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely. Prometax transdermal patches may cause fainting or severe confusion. If you feel faint or confused do not drive, use machines or perform any other tasks that require your attention.

3. How to use Prometax

Always use Prometax transdermal patches exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

IMPORTANT:
- **Take off the previous patch before putting ONE new patch on.**
- **Only one patch per day.**
- **Do not cut the patch into pieces.**
- **Press the patch firmly in place for at least 30 seconds using the palm of the hand.**

How to start treatment
Your doctor will tell you which Prometax transdermal patch is most suitable for you.
- Treatment usually starts with Prometax 4.6 mg/24 h.
- The recommended usual daily dose is Prometax 9.5 mg/24 h. If well tolerated, the treating physician may consider increasing the dose to 13.3 mg/24 h.
- Only wear one Prometax patch at a time and replace the patch with a new one after 24 hours.

During the course of the treatment your doctor may adjust the dose to suit your individual needs.

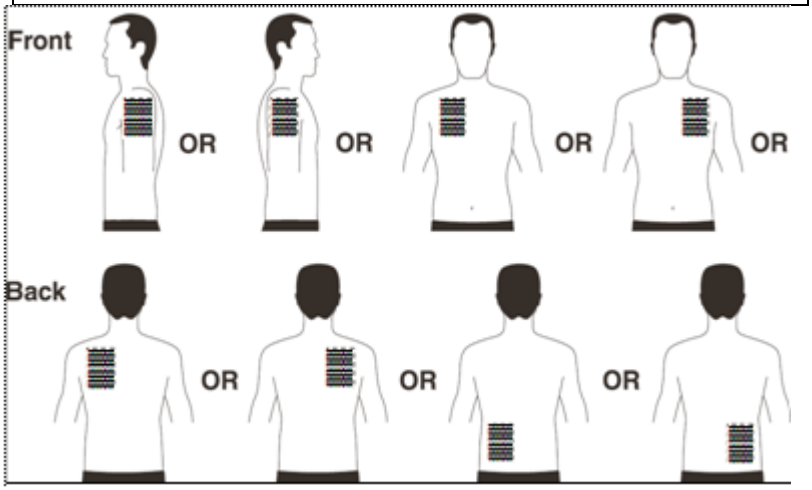
If you have not applied a patch for more than three days, do not apply the next one before you have talked to your doctor. Transdermal patch treatment can be resumed at the same dose if treatment is not interrupted for more than three days. Otherwise your doctor will restart your treatment on Prometax 4.6 mg/24 h.

Prometax can be used with food, drink and alcohol.

Where to apply your Prometax transdermal patch

- Before you apply a patch, make sure that your skin is clean, dry and hairless, free of any powder, oil, moisturiser or lotion that could keep the patch from sticking to your skin properly, free of cuts, rashes and/or irritations.
- **Carefully remove any existing patch before putting on a new one.** Having multiple patches on your body could expose you to an excessive amount of this medicine which could be potentially dangerous.
- Apply **ONE** patch per day to **ONLY ONE** of the possible locations shown in the following diagrams:
  - left upper arm **or** right upper arm
  - left upper chest **or** right upper chest **(avoid breast)**
  - left upper back **or** right upper back
  - left lower back **or** right lower back

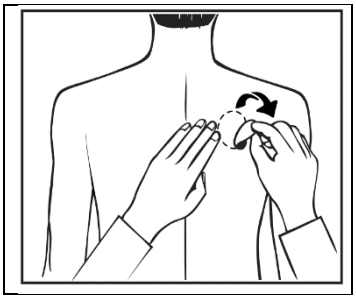
Every 24 hours take off the previous patch before putting ONE new patch on to ONLY ONE of the following possible locations.



When changing the patch, you must remove the previous day's patch before you apply the new one to a different location of skin each time (for example on the right side of your body one day, then on the left side the next day, and on your upper body one day, then on your lower body the next day). Do not apply a new patch to the same skin area twice within 14 days.

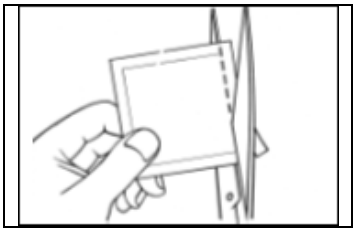
How to apply your Prometax transdermal patch
Prometax patches are thin, opaque, plastic patches that stick to the skin. Each patch is sealed in a sachet that protects it until you are ready to put it on. Do not open the sachet or remove a patch until just before you apply it.

Carefully remove the existing patch before putting on a new one.

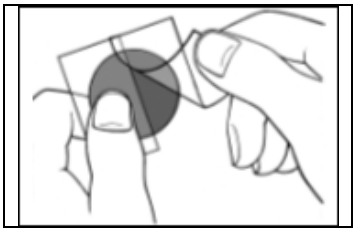


For patients starting treatment for the first time and for patients restarting Prometax after treatment interruption, please begin with the second picture.

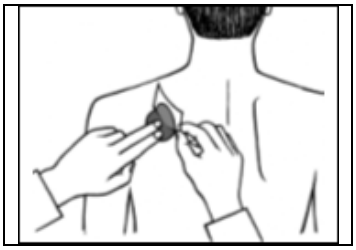
- Each patch is sealed in its own protective sachet.
  You should only open the sachet when you are ready to apply the patch.
  Cut the sachet along the dotted line with scissors and remove the patch from the sachet.



- A protective liner covers the sticky side of the patch.
  Peel off one side of the protective liner and do not touch the sticky part of the patch with the fingers.

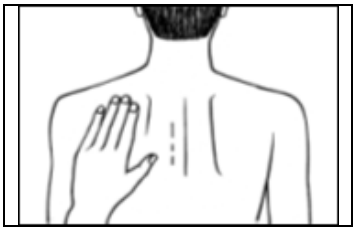


- Put the sticky side of the patch on the upper or lower back, upper arm or chest and then peel off the second side of the protective liner.



- Then press the patch firmly in place for at least 30 seconds using the palm of the hand to make sure that the edges stick well.

If it helps you, you may write, for example, the day of the week, on the patch with a thin ball point pen.



The patch should be worn continuously until it is time to replace it with a new one. You may wish to experiment with different locations when applying a new patch, to find ones that are most comfortable for you and where clothing will not rub on the patch.

How to remove your Prometax transdermal patch
Gently pull at one edge of the patch to remove it slowly from the skin. In case the adhesive residue is left over on your skin, gently soak the area with warm water and mild soap or use baby oil to remove it. Alcohol or other dissolving liquids (nail polish remover or other solvents) should not be used.

You should wash your hands with soap and water after removing the patch. In case of contact with eyes or if the eyes become red after handling the patch, rinse immediately with plenty of water and seek medical advice if symptoms do not resolve.

Can you wear your Prometax transdermal patch when you are bathing, swimming, or in the sun?

- Bathing, swimming or showering should not affect the patch. Make sure the patch does not loosen during these activities.
- Do not expose the patch to any external heat sources (e.g. excessive sunlight, saunas, solarium) for long periods of time.

What to do if a patch falls off

If a patch falls off, apply a new one for the rest of the day, then replace it at the same time as usual the next day.

When and for how long to apply your Prometax transdermal patch

- To benefit from treatment, you must apply a new patch every day, preferably at the same time of day.
- Only wear one Prometax patch at a time and replace the patch with a new one after 24 hours.

If you use more Prometax than you should

If you accidentally apply more than one patch, remove all the patches from your skin, then inform your doctor that you have accidentally applied more than one patch. You may require medical attention. Some people who have accidentally taken too much Prometax 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 use Prometax

If you find you have forgotten to apply a patch, apply one immediately. You may apply the next patch at the usual time the next day. Do not apply two patches to make up for the one that you missed.

If you stop using Prometax

Tell your doctor or pharmacist if you stop using the patch.

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

4. Possible side effects

Like all medicines, Prometax transdermal patches 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.

Take off your patch and tell your doctor straight away, if you notice any of the following side effects which could become serious:

Common (may affect up to 1 in 10 people)

- Loss of appetite
- Feeling dizzy
- Feeling agitated or sleepy
- Urinary incontinence (inability to retain adequate urine)

Uncommon (may affect up to 1 in 100 people)
- Problems with your heartbeat such as slow heartbeat
- Seeing things that are not really there (hallucinations)
- Stomach ulcer
- Dehydration (losing too much fluid)
- Hyperactivity (high level of activity, restlessness)
- Aggression

Rare (may affect up to 1 in 1,000 people)
- Falling

Very rare (may affect up to 1 in 10,000 people)
- Stiff arms or legs
- Trembling hands

Not known (frequency cannot be estimated from the available data)
- Allergic reaction where the patch was used, such as blisters or inflamed skin
- The signs of Parkinson's disease get worse – such as tremor, stiffness and shuffling
- Inflammation of the pancreas – signs include serious upper stomach pain, often with feeling sick (nausea) or being sick (vomiting)
- Fast or uneven heartbeat
- High blood pressure
- Fits (seizures)
- 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)
- Changes in tests which show how well the liver is working
- Feeling restless
- Nightmares

Take off your patch and tell your doctor straight away, if you notice any of the side effects above.

Other side effects seen with Prometax capsules or oral solution and which may occur with the patch:

Common (may affect up to 1 in 10 people)
- Too much saliva
- Loss of appetite
- Feeling restless
- Generally feeling unwell
- Trembling or feeling confused
- Increased sweating

Uncommon (may affect up to 1 in 100 people)
- Uneven heart rate (e.g. fast heart rate)
- Difficulty sleeping
- Accidental falls

Rare (may affect up to 1 in 1,000 people)
- Fits (seizures)
- Ulcer in the intestine
- Chest pain – this may be caused by heart spasm

Very rare (may affect up to 1 in 10,000 people)
- High blood pressure
- Inflammation of the pancreas – the signs include serious upper stomach pain, often with feeling sick (nausea) or being sick (vomiting)
- Bleeding in the gut – shows as blood in stools or when being sick
- Seeing things that are not there (hallucinations)
- Some people who have been violently sick have had tearing of the tube that connects your mouth with your stomach (oesophagus)

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 Prometax

- 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 carton and sachet after EXP. The expiry date refers to the last day of that month.
- Do not store above 25°C.
- Keep the transdermal patch in the sachet until use.
- Do not use any patch that is damaged or shows signs of tampering.
- After removing a patch, fold it in half with the sticky sides on the inside and press them together. Return the used patch to its sachet and dispose of it in such a way that children cannot handle it. Do not touch your eyes with your fingers and wash your hands with soap and water after removing the patch. 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 Prometax contains
- The active substance is rivastigmine.
  - Prometax 4.6 mg/24 h transdermal patches: Each patch releasing 4.6 mg of rivastigmine per 24 hours is 5 cm^2 and contains 9 mg of rivastigmine.
  - Prometax 9.5 mg/24 h transdermal patches: Each patch releasing 9.5 mg of rivastigmine per 24 hours is 10 cm^2 and contains 18 mg of rivastigmine.
  - Prometax 13.3 mg/24 h transdermal patches: Each patch releasing 13.3 mg of rivastigmine per 24 hours is 15 cm^2 and contains 27 mg of rivastigmine.

- The other ingredients are polyethylene terephthalate film lacquered, alpha-tocopherol, poly(butylmethacrylate, methylmethacrylate), acrylic copolymer, silicone oil, dimethicone, polyester film fluoropolymer-coated.

What Prometax looks like and contents of the pack
Each transdermal patch is a thin patch consisting of three layers. The outer layer is beige and labelled with the following:
- "Prometax", "4.6 mg/24 h" and "AMCX",
- "Prometax", "9.5 mg/24 h" and "BHDI",
- "Prometax", "13.3 mg/24 h" and "CNFU".

One transdermal patch is sealed in one sachet. The patches are available in packs containing 7 or 30 sachets and in multipacks containing 60 or 90 sachets. Not all pack sizes may be marketed in your country.

Marketing Authorisation Holder
Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

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

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

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

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Bulgaria EOOD
Тел.: +359 2 489 98 28

Česká republika
Sandoz s.r.o.
Tel: +420 221 421 658

Danmark
Sandoz A/S
Tlf: +45 63 95 10 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
SIA Novartis Baltics Eesti filiaal
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

Lietuva
SIA Novartis Baltics Lietuvos filialas
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma GmbH
Tél/Tel: +49 911 273 0

Magyarország
Novartis Hungária Kft.
Tel.: +36 1 457 65 00

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Sandoz B.V.
Tel: +31 36 52 41 600

Norge
Sandoz A/S
Tlf: +45 63 95 10 00

Österreich
Sandoz GmbH
Tel: +43 5 33 8200

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Sandoz S.p.A.
Tel: +39 02 96 54 3483

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
SIA Novartis Baltics
Tel: +371 67 887 070

Portugal
Laboratório Normal - Produtos Farmacêuticos, Lda.
Tel: +351 21 000 8600

România
Sandoz SRL Romania
Tel: +40 21 40751 83

Slovenija
Lek Pharmaceuticals d.d.
Tel: +386 1 580 33 27

Slovenská republika
Sandoz d.d. organizačná zložka
Tel: + 421 2 4820 0600

Suomi/Finland
Sandoz A/S
Puh/Tel: +45 6 395 10 00

Sverige
Sandoz A/S
Tel: +45 6 395 10 00

United Kingdom (Northern Ireland)
Novartis Ireland Limited
Tel: +44 1276 698020

This leaflet was last revised in

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