ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT
Exelon 1.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains rivastigmine hydrogen tartrate corresponding to 1.5 mg rivastigmine.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard capsules
Off-white to slightly yellow powder in a capsule with yellow cap and yellow body, with red imprint “EXELON 1.5 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.

**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, Exelon 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 Exelon in the paediatric population in the treatment of Alzheimer’s disease.

### 4.3 Contraindications

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

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

### 4.4 Special warnings and precautions for use

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

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

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see section 4.3).
Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

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

Patients and caregivers should be instructed accordingly.

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

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

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

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

Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).

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

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

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

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

The use of rivastigmine in patients with severe dementia of Alzheimer’s disease or associated with Parkinson’s disease, other types of dementia or other types of memory impairment (e.g. age-related cognitive decline) has not been investigated and therefore use in these patient populations is not recommended.
Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening (including bradykinesia, dyskinesia, gait abnormality) and an increased incidence or severity of tremor have been observed in patients with dementia associated with Parkinson’s disease (see section 4.8). These events led to the discontinuation of rivastigmine in some cases (e.g. discontinuations due to tremor 1.7% on rivastigmine vs 0% on placebo). Clinical monitoring is recommended for these adverse reactions.

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

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

### 4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

### 4.6 Fertility, pregnancy and lactation

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated list of adverse reactions
Adverse reactions in Table 1 and Table 2 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥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 Exelon.

Table 1

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Urinary infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Not known</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Not known</td>
</tr>
<tr>
<td>Nervous system disorders</td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
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<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Rare</td>
</tr>
<tr>
<td>Very rare</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th>Rare</th>
<th>Angina pectoris</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia)</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Sick sinus syndrome</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th>Very rare</th>
<th>Hypertension</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Very common</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Diarrhoea</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Abdominal pain and dyspepsia</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>Gastric and duodenal ulcers</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Gastrointestinal haemorrhage</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th>Uncommon</th>
<th>Elevated liver function tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Hepatitis</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th>Common</th>
<th>Hyperhydrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Rash</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Pruritus, allergic dermatitis (disseminated)</td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th>Common</th>
<th>Fatigue and asthenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Malaise</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Fall</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Common</th>
<th>Weight loss</th>
</tr>
</thead>
</table>

7
The following additional adverse reactions have been observed with Exelon 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 Exelon capsules.

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Common</td>
<td>Dehydration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Common</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Common</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Common</td>
<td>Hallucination, visual</td>
</tr>
<tr>
<td>Common</td>
<td>Depression</td>
</tr>
<tr>
<td>Not known</td>
<td>Aggression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Tremor</td>
</tr>
<tr>
<td>Common</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Common</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Common</td>
<td>Headache</td>
</tr>
<tr>
<td>Common</td>
<td>Parkinson’s disease (worsening)</td>
</tr>
<tr>
<td>Common</td>
<td>Bradykinesia</td>
</tr>
<tr>
<td>Common</td>
<td>Dyskinesia</td>
</tr>
<tr>
<td>Common</td>
<td>Hypokinesia</td>
</tr>
<tr>
<td>Common</td>
<td>Cogwheel rigidity</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dystonia</td>
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</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Atrioventricular block</td>
</tr>
<tr>
<td>Not known</td>
<td>Sick sinus syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypotension</td>
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</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Nausea</td>
</tr>
<tr>
<td>Very common</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Common</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Common</td>
<td>Abdominal pain and dyspepsia</td>
</tr>
<tr>
<td>Common</td>
<td>Salivary hypersecretion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Hyperhydrosis</td>
</tr>
<tr>
<td>Not known</td>
<td>Allergic dermatitis (disseminated)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Fall</td>
</tr>
<tr>
<td>Common</td>
<td>Fatigue and asthenia</td>
</tr>
<tr>
<td>Common</td>
<td>Gait disturbance</td>
</tr>
<tr>
<td>Common</td>
<td>Parkinson gait</td>
</tr>
</tbody>
</table>
The following additional adverse reaction has been observed in a study of patients with dementia associated with Parkinson’s disease treated with Exelon transdermal patches: agitation (common).

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

### Table 3

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

**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

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

*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

<table>
<thead>
<tr>
<th>Dementia associated with Parkinson’s Disease</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
<th>ADCS-CGIC Exelon</th>
<th>ADCS-CGIC Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT + RDO population</td>
<td>(n=329)</td>
<td>(n=161)</td>
<td>(n=329)</td>
<td>(n=165)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>23.8 ± 10.2</td>
<td>24.3 ± 10.5</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>2.1 ± 8.2</td>
<td>-0.7 ± 7.5</td>
<td>3.8 ± 1.4</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>2.88(^1)</td>
<td>n/a</td>
<td>n/a</td>
<td>0.007(^2)</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>&lt;0.001(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT - LOCF population</td>
<td>(n=287)</td>
<td>(n=154)</td>
<td>(n=289)</td>
<td>(n=158)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>24.0 ± 10.3</td>
<td>24.5 ± 10.6</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>2.5 ± 8.4</td>
<td>-0.8 ± 7.5</td>
<td>3.7 ± 1.4</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>3.54(^1)</td>
<td>n/a</td>
<td>n/a</td>
<td>&lt;0.001(^2)</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>&lt;0.001(^1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) 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>
<thead>
<tr>
<th>Table 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dementia associated with Parkinson’s Disease</strong></td>
</tr>
<tr>
<td><strong>Patients with visual hallucinations</strong></td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
</tr>
<tr>
<td>p-value versus placebo</td>
</tr>
<tr>
<td><strong>Patients with moderate dementia (MMSE 10-17)</strong></td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
</tr>
<tr>
<td>p-value versus placebo</td>
</tr>
</tbody>
</table>

<sup>1</sup> 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 Exelon 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<sub>max</sub>) by 90 min and lowers C<sub>max</sub> 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.
Biotranformation
Rivastigmine is rapidly and extensively metabolised (half-life in plasma approximately 1 hour), primarily via cholinesterase-mediated hydrolysis to the decarbamylated metabolite. In vitro, this metabolite shows minimal inhibition of acetylcholinesterase (<10%).

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

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

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

Older people
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\text{\textsubscript{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\text{\textsubscript{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\text{\textsubscript{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\textsuperscript{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
Hypermellose
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.
- HDPE bottles with plastic closure with induction innerseal. Each bottle contains 250 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom
8. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/066/001-3
EU/1/98/066/014

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 12 May 1998
Date of latest renewal: 12 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

Exelon 3.0 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

Off-white to slightly yellow powder in a capsule with orange cap and orange body, with red imprint “EXELON 3 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.

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, Exelon 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 Exelon in the paediatric population in the treatment of Alzheimer’s disease.

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

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

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

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see section 4.3).
Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

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

Patients and caregivers should be instructed accordingly.

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

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

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

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

Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).

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

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

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

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

The use of rivastigmine in patients with severe dementia of Alzheimer’s disease or associated with Parkinson’s disease, other types of dementia or other types of memory impairment (e.g. age-related cognitive decline) has not been investigated and therefore use in these patient populations is not recommended.
Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening (including bradykinesia, dyskinesia, gait abnormality) and an increased incidence or severity of tremor have been observed in patients with dementia associated with Parkinson’s disease (see section 4.8). These events led to the discontinuation of rivastigmine in some cases (e.g. discontinuations due to tremor 1.7% on rivastigmine vs 0% on placebo). Clinical monitoring is recommended for these adverse reactions.

**Special populations**

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

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

### 4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated list of adverse reactions
Adverse reactions in Table 1 and Table 2 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥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 Exelon.

Table 1

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Urinary infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Not known</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
</tr>
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<td>Uncommon</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Not known</td>
</tr>
</tbody>
</table>
### Nervous system disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Common</td>
<td>Headache</td>
</tr>
<tr>
<td>Common</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Common</td>
<td>Tremor</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Syncope</td>
</tr>
<tr>
<td>Rare</td>
<td>Seizures</td>
</tr>
<tr>
<td>Very rare</td>
<td>Extrapyramidal symptoms (including worsening of</td>
</tr>
<tr>
<td></td>
<td>Parkinson’s disease)</td>
</tr>
</tbody>
</table>

### Cardiac disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Very rare</td>
<td>Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia)</td>
</tr>
<tr>
<td>Not known</td>
<td>Sick sinus syndrome</td>
</tr>
</tbody>
</table>

### Vascular disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

### Gastrointestinal disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Nausea</td>
</tr>
<tr>
<td>Very common</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Very common</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Common</td>
<td>Abdominal pain and dyspepsia</td>
</tr>
<tr>
<td>Rare</td>
<td>Gastric and duodenal ulcers</td>
</tr>
<tr>
<td>Very rare</td>
<td>Gastrointestinal haemorrhage</td>
</tr>
<tr>
<td>Very rare</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Not known</td>
<td>Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).</td>
</tr>
</tbody>
</table>

### Hepatobiliary disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Elevated liver function tests</td>
</tr>
<tr>
<td>Not known</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Hyperhydrosis</td>
</tr>
<tr>
<td>Rare</td>
<td>Rash</td>
</tr>
<tr>
<td>Not known</td>
<td>Pruritus, allergic dermatitis (disseminated)</td>
</tr>
</tbody>
</table>

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Fatigue and asthenia</td>
</tr>
<tr>
<td>Common</td>
<td>Malaise</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Fall</td>
</tr>
</tbody>
</table>

### Investigations

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Weight loss</td>
</tr>
</tbody>
</table>
The following additional adverse reactions have been observed with Exelon 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 Exelon capsules.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
</tr>
<tr>
<td>Common Decreased appetite</td>
</tr>
<tr>
<td>Common Dehydration</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
</tr>
<tr>
<td>Common Insomnia</td>
</tr>
<tr>
<td>Common Anxiety</td>
</tr>
<tr>
<td>Common Restlessness</td>
</tr>
<tr>
<td>Common Hallucination, visual</td>
</tr>
<tr>
<td>Common Depression</td>
</tr>
<tr>
<td>Not known Aggression</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td>Very common Tremor</td>
</tr>
<tr>
<td>Common Dizziness</td>
</tr>
<tr>
<td>Common Somnolence</td>
</tr>
<tr>
<td>Common Headache</td>
</tr>
<tr>
<td>Common Parkinson’s disease (worsening)</td>
</tr>
<tr>
<td>Common Bradykinesia</td>
</tr>
<tr>
<td>Common Dyskinesia</td>
</tr>
<tr>
<td>Common Hypokinesia</td>
</tr>
<tr>
<td>Common Cogwheel rigidity</td>
</tr>
<tr>
<td>Uncommon Dystonia</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
</tr>
<tr>
<td>Common Bradycardia</td>
</tr>
<tr>
<td>Uncommon Atrial Fibrillation</td>
</tr>
<tr>
<td>Uncommon Atrioventricular block</td>
</tr>
<tr>
<td>Not known Sick sinus syndrome</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
</tr>
<tr>
<td>Common Hypertension</td>
</tr>
<tr>
<td>Uncommon Hypotension</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
</tr>
<tr>
<td>Very common Nausea</td>
</tr>
<tr>
<td>Very common Vomiting</td>
</tr>
<tr>
<td>Common Diarrhoea</td>
</tr>
<tr>
<td>Common Abdominal pain and dyspepsia</td>
</tr>
<tr>
<td>Common Salivary hypersecretion</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
</tr>
<tr>
<td>Not known Hepatitis</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
</tr>
<tr>
<td>Common Hyperhydrosis</td>
</tr>
<tr>
<td>Not known Allergic dermatitis (disseminated)</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
</tr>
<tr>
<td>Very common Fall</td>
</tr>
<tr>
<td>Common Fatigue and asthenia</td>
</tr>
<tr>
<td>Common Gait disturbance</td>
</tr>
<tr>
<td>Common Parkinson gait</td>
</tr>
</tbody>
</table>
The following additional adverse reaction has been observed in a study of patients with dementia associated with Parkinson’s disease treated with Exelon transdermal patches: agitation (common).

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

### Table 3

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

**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

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

*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

<table>
<thead>
<tr>
<th>Dementia associated with Parkinson’s Disease</th>
<th>ADAS-Cog Exelon (n=329)</th>
<th>ADAS-Cog Placebo (n=161)</th>
<th>ADCS-CGIC Exelon (n=329)</th>
<th>ADCS-CGIC Placebo (n=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline ± SD</td>
<td>23.8 ± 10.2</td>
<td>24.3 ± 10.5</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>2.1 ± 8.2</td>
<td>-0.7 ± 7.5</td>
<td>3.8 ± 1.4</td>
<td>4.3 ± 1.5</td>
</tr>
</tbody>
</table>

Adjusted treatment difference
p-value versus placebo

ITT + RDO population
2.88<sup>1</sup> <0.001<sup>1</sup> n/a 0.007<sup>2</sup>

ITT - LOCF population
3.54<sup>1</sup> <0.001<sup>1</sup> n/a <0.001<sup>2</sup>

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

<table>
<thead>
<tr>
<th>Dementia associated with Parkinson’s Disease</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT + RDO population</td>
<td>(n=107)</td>
<td>(n=60)</td>
<td>(n=220)</td>
<td>(n=101)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>25.4 ± 9.9</td>
<td>27.4 ± 10.4</td>
<td>23.1 ± 10.4</td>
<td>22.5 ± 10.1</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td><strong>1.0 ± 9.2</strong></td>
<td>-2.1 ± 8.3</td>
<td><strong>2.6 ± 7.6</strong></td>
<td>0.1 ± 6.9</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>4.27¹</td>
<td>0.002¹</td>
<td>2.09¹</td>
<td>0.015¹</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with visual hallucinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without visual hallucinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT + RDO population</td>
<td>(n=87)</td>
<td>(n=44)</td>
<td>(n=237)</td>
<td>(n=115)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>32.6 ± 10.4</td>
<td>33.7 ± 10.3</td>
<td>20.6 ± 7.9</td>
<td>20.7 ± 7.9</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td><strong>2.6 ± 9.4</strong></td>
<td>-1.8 ± 7.2</td>
<td><strong>1.9 ± 7.7</strong></td>
<td>-0.2 ± 7.5</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>4.73¹</td>
<td>0.002¹</td>
<td>2.14¹</td>
<td>0.010¹</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with moderate dementia (MMSE 10-17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with mild dementia (MMSE 18-24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 Exelon in all subsets of the paediatric population in the treatment of Alzheimer’s disease 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<sub>max</sub>) by 90 min and lowers C<sub>max</sub> and increases AUC by approximately 30%.

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

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

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

**Elimination**

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

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

**Older people**

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 $C_{\text{max}}$ 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**

$C_{\text{max}}$ 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 $C_{\text{max}}$ 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
Hypermellose
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.
- HDPE bottles with plastic closure with induction innerseal. Each bottle contains 250 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/004-6
EU/1/98/066/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 May 1998
Date of latest renewal: 12 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

Exelon 4.5 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

Off-white to slightly yellow powder in a capsule with red cap and red body, with white imprint “EXELON 4,5 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.

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, Exelon 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 Exelon in the paediatric population in the treatment of Alzheimer’s disease.

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

Prevalent 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, Exelon has been discontinued (see section 4.8).

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

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

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

Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).

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

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

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

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

The use of rivastigmine in patients with severe dementia of Alzheimer’s disease or associated with Parkinson’s disease, other types of dementia or other types of memory impairment (e.g. age-related cognitive decline) has not been investigated and therefore use in these patient populations is not recommended.
Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening (including bradykinesia, dyskinesia, gait abnormality) and an increased incidence or severity of tremor have been observed in patients with dementia associated with Parkinson’s disease (see section 4.8). These events led to the discontinuation of rivastigmine in some cases (e.g. discontinuations due to tremor 1.7% on rivastigmine vs 0% on placebo). Clinical monitoring is recommended for these adverse reactions.

**Special populations**

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

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

**4.5 Interaction with other medicinal products and other forms of interaction**

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

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

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

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

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

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

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

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

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

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

4.8 Undesirable effects

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

Tabulated list of adverse reactions
Adverse reactions in Table 1 and Table 2 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥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 Exelon.

Table 1

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Urinary infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Not known</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Not known</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
</tr>
<tr>
<td>------------------------------</td>
</tr>
<tr>
<td><strong>Very common</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cardiac disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
<td>Angina pectoris</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia)</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>Sick sinus syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Vascular disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very rare</strong></td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Gastrointestinal disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very common</strong></td>
<td>Nausea</td>
</tr>
<tr>
<td><strong>Very common</strong></td>
<td>Vomiting</td>
</tr>
<tr>
<td><strong>Very common</strong></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Abdominal pain and dyspepsia</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Gastric and duodenal ulcers</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Gastrointestinal haemorrhage</td>
</tr>
<tr>
<td><strong>Very rare</strong></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Hepatobiliary disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon</strong></td>
<td>Elevated liver function tests</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Skin and subcutaneous tissue disorders</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Hyperhydrosis</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
<td>Rash</td>
</tr>
<tr>
<td><strong>Not known</strong></td>
<td>Pruritus, allergic dermatitis (disseminated)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>General disorders and administration site conditions</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Fatigue and asthenia</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Malaise</td>
</tr>
<tr>
<td><strong>Uncommon</strong></td>
<td>Fall</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Investigations</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>Weight loss</td>
</tr>
</tbody>
</table>
The following additional adverse reactions have been observed with Exelon 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 Exelon capsules.

Table 2

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Common</th>
<th>Decreased appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td></td>
<td>Dehydration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Restlessness</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Hallucination, visual</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
<td>Aggression</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Very common</td>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Somnolence</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Parkinson’s disease (worsening)</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Bradykinesia</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Dyskinesia</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Hypokinesia</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Cogwheel rigidity</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td>Dystonia</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Cardiac disorders</th>
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<tbody>
<tr>
<td>Common</td>
<td></td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td>Atrioventricular block</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
<td>Sick sinus syndrome</td>
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<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
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<tbody>
<tr>
<td>Common</td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td>Hypotension</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
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<tbody>
<tr>
<td>Very common</td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td>Very common</td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Abdominal pain and dyspepsia</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Salivary hypersecretion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td></td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td></td>
<td>Hyperhydrosis</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
<td>Allergic dermatitis (disseminated)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td></td>
<td>Fall</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Fatigue and asthenia</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Gait disturbance</td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Parkinson gait</td>
</tr>
</tbody>
</table>
The following additional adverse reaction has been observed in a study of patients with dementia associated with Parkinson’s disease treated with Exelon transdermal patches: agitation (common).

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

### Table 3

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

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**

<table>
<thead>
<tr>
<th>Response Measure</th>
<th>Patients with Clinically Significant Response (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intent to Treat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog: improvement of at least 4 points</td>
<td>Rivastigmine 6–12 mg N=473</td>
<td>21***</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Placebo N=472</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>CIBIC-Plus: improvement</td>
<td>Rivastigmine 6–12 mg N=379</td>
<td>25***</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Placebo N=444</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>PDS: improvement of at least 10%</td>
<td>Rivastigmine</td>
<td>26***</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>30***</td>
<td>18</td>
</tr>
<tr>
<td>At least 4 points improvement on ADAS-Cog with no worsening on CIBIC-Plus and PDS</td>
<td>Rivastigmine 6–12 mg N=379</td>
<td>10*</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>12**</td>
<td>6</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Dementia associated with Parkinson’s Disease</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
<th>ADCS-CGIC Exelon</th>
<th>ADCS-CGIC Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT + RDO population</td>
<td>(n=329)</td>
<td>(n=161)</td>
<td>(n=329)</td>
<td>(n=165)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>23.8 ± 10.2</td>
<td>24.3 ± 10.5</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td><strong>2.1 ± 8.2</strong></td>
<td>-0.7 ± 7.5</td>
<td><strong>3.8 ± 1.4</strong></td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>2.88(^1)</td>
<td>n/a</td>
<td>n/a</td>
<td>0.007(^2)</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>&lt;0.001(^1)</td>
<td>n/a</td>
<td>0.007(^2)</td>
<td></td>
</tr>
<tr>
<td>ITT - LOCF population</td>
<td>(n=287)</td>
<td>(n=154)</td>
<td>(n=289)</td>
<td>(n=158)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>24.0 ± 10.3</td>
<td>24.5 ± 10.6</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td><strong>2.5 ± 8.4</strong></td>
<td>-0.8 ± 7.5</td>
<td><strong>3.7 ± 1.4</strong></td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>3.54(^1)</td>
<td>n/a</td>
<td>n/a</td>
<td>&lt;0.001(^2)</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>&lt;0.001(^1)</td>
<td>n/a</td>
<td>&lt;0.001(^2)</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) 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

<table>
<thead>
<tr>
<th>Dementia associated with Parkinson’s Disease</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT + RDO population</td>
<td>Patients with visual hallucinations</td>
<td>Patients without visual hallucinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT + RDO population</td>
<td>(n=107)</td>
<td>(n=60)</td>
<td>(n=220)</td>
<td>(n=101)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>25.4 ± 9.9</td>
<td>27.4 ± 10.4</td>
<td>23.1 ± 10.4</td>
<td>22.5 ± 10.1</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>1.0 ± 9.2</td>
<td>-2.1 ± 8.3</td>
<td>2.6 ± 7.6</td>
<td>0.1 ± 6.9</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>4.27&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.002&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.09&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.015&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with moderate dementia (MMSE 10-17)</td>
<td>(n=87)</td>
<td>(n=44)</td>
<td>(n=237)</td>
<td>(n=115)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>32.6 ± 10.4</td>
<td>33.7 ± 10.3</td>
<td>20.6 ± 7.9</td>
<td>20.7 ± 7.9</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>2.6 ± 9.4</td>
<td>-1.8 ± 7.2</td>
<td>1.9 ± 7.7</td>
<td>-0.2 ± 7.5</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>4.73&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.002&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2.14&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.010&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> 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 Exelon in all subsets of the paediatric population in the treatment of Alzheimer’s disease 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<sub>max</sub>) by 90 min and lowers C<sub>max</sub> and increases AUC by approximately 30%.

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

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

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

**Elimination**

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

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

**Older people**

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\text{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\text{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\text{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
Hypermellose
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.
- HDPE bottles with plastic closure with induction innerseal. Each bottle contains 250 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/007-9
EU/1/98/066/016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 May 1998
Date of latest renewal: 12 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**

Exelon 6.0 mg hard capsules

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

Off-white to slightly yellow powder in a capsule with red cap and orange body, with red imprint “EXELON 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.

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, Exelon 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 Exelon in the paediatric population in the treatment of Alzheimer’s disease.

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

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

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

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see section 4.3).
Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

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

Patients and caregivers should be instructed accordingly.

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

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

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

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

Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).

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

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

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

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

The use of rivastigmine in patients with severe dementia of Alzheimer’s disease or associated with Parkinson’s disease, other types of dementia or other types of memory impairment (e.g. age-related cognitive decline) has not been investigated and therefore use in these patient populations is not recommended.
Like other cholinomimetics, rivastigmine may exacerbate or induce extrapyramidal symptoms. Worsening (including bradykinesia, dyskinesia, gait abnormality) and an increased incidence or severity of tremor have been observed in patients with dementia associated with Parkinson’s disease (see section 4.8). These events led to the discontinuation of rivastigmine in some cases (e.g. discontinuations due to tremor 1.7% on rivastigmine vs 0% on placebo). Clinical monitoring is recommended for these adverse reactions.

**Special populations**

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

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

### 4.5 Interaction with other medicinal products and other forms of interaction

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

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

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

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

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

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

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

Tabulated list of adverse reactions
Adverse reactions in Table 1 and Table 2 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥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 Exelon.

Table 1

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Metabolism and nutrition disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Urinary infection</td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td>Decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td></td>
</tr>
<tr>
<td>Common Nightmares</td>
<td></td>
</tr>
<tr>
<td>Common Agitation</td>
<td></td>
</tr>
<tr>
<td>Common Confusion</td>
<td></td>
</tr>
<tr>
<td>Common Anxiety</td>
<td></td>
</tr>
<tr>
<td>Uncommon Insomnia</td>
<td></td>
</tr>
<tr>
<td>Uncommon Depression</td>
<td></td>
</tr>
<tr>
<td>Very rare Hallucinations</td>
<td></td>
</tr>
<tr>
<td>Not known Aggression, restlessness</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common Dizziness</td>
</tr>
<tr>
<td>Common Headache</td>
</tr>
<tr>
<td>Common Somnolence</td>
</tr>
<tr>
<td>Common Tremor</td>
</tr>
<tr>
<td>Uncommon Syncope</td>
</tr>
<tr>
<td>Rare Seizures</td>
</tr>
<tr>
<td>Very rare Extrapyramidal symptoms (including worsening of Parkinson’s disease)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare Angina pectoris</td>
</tr>
<tr>
<td>Very rare Cardiac arrhythmia (e.g. bradycardia, atrio-ventricular block, atrial fibrillation and tachycardia)</td>
</tr>
<tr>
<td>Not known Sick sinus syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare Hypertension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common Nausea</td>
</tr>
<tr>
<td>Very common Vomiting</td>
</tr>
<tr>
<td>Very common Diarrhoea</td>
</tr>
<tr>
<td>Common Abdominal pain and dyspepsia</td>
</tr>
<tr>
<td>Rare Gastric and duodenal ulcers</td>
</tr>
<tr>
<td>Very rare Gastrointestinal haemorrhage</td>
</tr>
<tr>
<td>Very rare Pancreatitis</td>
</tr>
<tr>
<td>Not known Some cases of severe vomiting were associated with oesophageal rupture (see section 4.4).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon Elevated liver function tests</td>
</tr>
<tr>
<td>Not known Hepatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Hyperhydrosis</td>
</tr>
<tr>
<td>Rare Rash</td>
</tr>
<tr>
<td>Not known Pruritus, allergic dermatitis (disseminated)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Fatigue and asthenia</td>
</tr>
<tr>
<td>Common Malaise</td>
</tr>
<tr>
<td>Uncommon Fall</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Weight loss</td>
</tr>
</tbody>
</table>
The following additional adverse reactions have been observed with Exelon 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 Exelon capsules.

**Table 2**

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Decreased appetite</th>
<th>Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Restlessness</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Hallucination, visual</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Aggression</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Tremor</td>
</tr>
<tr>
<td>Common</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Common</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Common</td>
<td>Headache</td>
</tr>
<tr>
<td>Common</td>
<td>Parkinson’s disease (worsening)</td>
</tr>
<tr>
<td>Common</td>
<td>Bradykinesia</td>
</tr>
<tr>
<td>Common</td>
<td>Dyskinesia</td>
</tr>
<tr>
<td>Common</td>
<td>Hypokinesia</td>
</tr>
<tr>
<td>Common</td>
<td>Cogwheel rigidity</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dystonia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Common</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Atroventricular block</td>
</tr>
<tr>
<td>Not known</td>
<td>Sick sinus syndrome</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Hypotension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Nausea</td>
</tr>
<tr>
<td>Very common</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Common</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Common</td>
<td>Abdominal pain and dyspepsia</td>
</tr>
<tr>
<td>Common</td>
<td>Salivary hypersecretion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Hepatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Hyperhydrosis</td>
</tr>
<tr>
<td>Not known</td>
<td>Allergic dermatitis (disseminated)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Fatigue and asthenia</td>
</tr>
<tr>
<td>Common</td>
<td>Gait disturbance</td>
</tr>
<tr>
<td>Common</td>
<td>Parkinson gait</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th></th>
</tr>
</thead>
</table>
The following additional adverse reaction has been observed in a study of patients with dementia associated with Parkinson’s disease treated with Exelon transdermal patches: agitation (common).

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

**Table 3**

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

**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 butrylycholinesterase 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 butrylycholinesterase 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

<table>
<thead>
<tr>
<th>Response Measure</th>
<th>Patients with Clinically Significant Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intent to Treat</td>
</tr>
<tr>
<td></td>
<td>Rivastigmine 6–12 mg N=473</td>
</tr>
<tr>
<td>ADAS-Cog: improvement of at least 4 points</td>
<td>21***</td>
</tr>
<tr>
<td>CIBIC-Plus: improvement</td>
<td>29***</td>
</tr>
<tr>
<td>PDS: improvement of at least 10%</td>
<td>26***</td>
</tr>
<tr>
<td>At least 4 points improvement on ADAS-Cog with no worsening on CIBIC-Plus and PDS</td>
<td>10*</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Dementia associated with Parkinson’s Disease</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
<th>ADCS-CGIC Exelon</th>
<th>ADCS-CGIC Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ITT + RDO population</strong></td>
<td>(n=329)</td>
<td>(n=161)</td>
<td>(n=329)</td>
<td>(n=165)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>23.8 ± 10.2</td>
<td>24.3 ± 10.5</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>2.1 ± 8.2</td>
<td>-0.7 ± 7.5</td>
<td>3.8 ± 1.4</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>Adjusted treatment difference p-value versus placebo</td>
<td>2.88&lt;sup&gt;1&lt;/sup&gt;</td>
<td>n/a</td>
<td>n/a</td>
<td>3.54&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>ITT - LOCF population</td>
<td>(n=287)</td>
<td>(n=154)</td>
<td>(n=289)</td>
<td>(n=158)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>24.0 ± 10.3</td>
<td>24.5 ± 10.6</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>2.5 ± 8.4</td>
<td>-0.8 ± 7.5</td>
<td>3.7 ± 1.4</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>Adjusted treatment difference p-value versus placebo</td>
<td>3.54&lt;sup&gt;1&lt;/sup&gt;</td>
<td>n/a</td>
<td>n/a</td>
<td>3.54&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> Based on ANCOVA with treatment and country as factors and baseline ADAS-Cog as a covariate. A positive change indicates improvement.
<sup>2</sup> 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

<table>
<thead>
<tr>
<th>Dementia associated with Parkinson’s Disease</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT + RDO population</td>
<td>(n=107)</td>
<td>(n=60)</td>
<td>(n=220)</td>
<td>(n=101)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>25.4 ± 9.9</td>
<td>27.4 ± 10.4</td>
<td>23.1 ± 10.4</td>
<td>22.5 ± 10.1</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>1.0 ± 9.2</td>
<td>-2.1 ± 8.3</td>
<td>2.6 ± 7.6</td>
<td>0.1 ± 6.9</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>4.27\textsuperscript{1}</td>
<td>0.002\textsuperscript{1}</td>
<td>2.09\textsuperscript{1}</td>
<td>0.015\textsuperscript{1}</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with visual hallucinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients without visual hallucinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT + RDO population</td>
<td>(n=87)</td>
<td>(n=44)</td>
<td>(n=237)</td>
<td>(n=115)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>32.6 ± 10.4</td>
<td>33.7 ± 10.3</td>
<td>20.6 ± 7.9</td>
<td>20.7 ± 7.9</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>2.6 ± 9.4</td>
<td>-1.8 ± 7.2</td>
<td>1.9 ± 7.7</td>
<td>-0.2 ± 7.5</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>4.73\textsuperscript{1}</td>
<td>0.002\textsuperscript{1}</td>
<td>2.14\textsuperscript{1}</td>
<td>0.010\textsuperscript{1}</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{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 Exelon 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\textsubscript{max}) by 90 min and lowers C\textsubscript{max} and increases AUC by approximately 30%.

Distribution

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

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

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

Elimination

Unchanged rivastigmine is not found in the urine; renal excretion of the metabolites is the major route of elimination. Following administration of $^{14}$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.

Older people

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 $C_{\text{max}}$ 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

$C_{\text{max}}$ 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 $C_{\text{max}}$ 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
Hypermellose
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.
- HDPE bottles with plastic closure with induction innerseal. Each bottle contains 250 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/010-12
EU/1/98/066/017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 May 1998
Date of latest renewal: 12 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

Exelon 2 mg/ml oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Clear, yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

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

Initial dose

1.5 mg twice a day.

Dose titration

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

If adverse reactions (e.g. nausea, vomiting, abdominal pain or loss of appetite), weight decrease or worsening of extrapyramidal symptoms (e.g. tremor) in patients with dementia associated with Parkinson’s disease are observed during treatment, these may respond to omitting one or more doses. If adverse reactions persist, the daily dose should be temporarily reduced to the previous well-tolerated dose or the treatment may be discontinued.
Maintenance dose
The effective dose is 3 to 6 mg twice a day; to achieve maximum therapeutic benefit patients should be maintained on their highest well tolerated dose. The recommended maximum daily dose is 6 mg twice a day.

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

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

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

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

Renal and hepatic impairment
No dose adjustment is necessary for patients with mild to moderate renal or hepatic impairment. However, due to increased exposure in these populations dosing recommendations to titrate according to individual tolerability should be closely followed as patients with clinically significant renal or hepatic impairment might experience more dose-dependent adverse reactions. Patients with severe hepatic impairment have not been studied, however, Exelon 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 Exelon in the paediatric population in the treatment of Alzheimer’s disease.

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

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

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

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

Allergic contact dermatitis should be suspected if application site reactions spread beyond the patch size, if there is evidence of a more intense local reaction (e.g. increasing erythema, oedema, papules, vesicles) and if symptoms do not significantly improve within 48 hours after patch removal. In these cases, treatment should be discontinued (see section 4.3).
Patients who develop application site reactions suggestive of allergic contact dermatitis to rivastigmine patch and who still require rivastigmine treatment should only be switched to oral rivastigmine after negative allergy testing and under close medical supervision. It is possible that some patients sensitised to rivastigmine by exposure to rivastigmine patch may not be able to take rivastigmine in any form.

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

Patients and caregivers should be instructed accordingly.

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

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

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

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

Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).

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

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

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

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

One of the excipients in Exelon oral solution is sodium benzoate. Benzoic acid is a mild irritant to the skin, eyes and mucous membrane.
The use of rivastigmine in patients with severe dementia of Alzheimer’s disease or associated with Parkinson’s disease, other types of dementia or other types of memory impairment (e.g. age-related cognitive decline) has not been investigated and therefore use in these patient populations is not recommended.

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

**Special populations**

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

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

**4.5 Interaction with other medicinal products and other forms of interaction**

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

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

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

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

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

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

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

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

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

4.7  Effects on ability to drive and use machines

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

4.8  Undesirable effects

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

**Tabulated list of adverse reactions**
Adverse reactions in Table 1 and Table 2 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥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 Exelon.

**Table 1**

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Urinary infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Anorexia</td>
</tr>
<tr>
<td>Common</td>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Not known</td>
<td>Dehydration</td>
</tr>
</tbody>
</table>
### Psychiatric disorders

- **Common**
  - Nightmares
  - Agitation
  - Confusion
  - Anxiety
  - Insomnia
  - Depression
- **Very rare**
  - Hallucinations
- **Not known**
  - Aggression, restlessness

### Nervous system disorders

- **Very common**
  - Dizziness
  - Headache
  - Somnolence
  - 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
  - Vomiting
  - 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
  - Malaise
- **Uncommon**
  - Fall

### Investigations

- **Common**
  - Weight loss
The following additional adverse reactions have been observed with Exelon 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 Exelon capsules.

**Table 2**

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Common</th>
<th>Decreased appetite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Restlessness</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Hallucination, visual</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Depression</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Not known</td>
<td>Aggression</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Very common</td>
<td>Tremor</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Parkinson’s disease (worsening)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Bradykinesia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Dyskinesia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Hypokinesia</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Cogwheel rigidity</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Common</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Atrioventricular block</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Not known</td>
<td>Sick sinus syndrome</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Common</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Nausea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Abdominal pain and dyspepsia</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Salivary hypersecretion</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common</td>
<td>Hyperhydrosis</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Not known</td>
<td>Allergic dermatitis (disseminated)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>Fall</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Fatigue and asthenia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Gait disturbance</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Common</td>
<td>Parkinson gait</td>
</tr>
</tbody>
</table>
The following additional adverse reaction has been observed in a study of patients with dementia associated with Parkinson’s disease treated with Exelon transdermal patches: agitation (common).

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

**Table 3**

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

**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**

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

*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

<table>
<thead>
<tr>
<th>Dementia associated with Parkinson’s Disease</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
<th>ADCS-CGIC Exelon</th>
<th>ADCS-CGIC Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT + RDO population</td>
<td>(n=329)</td>
<td>(n=161)</td>
<td>(n=329)</td>
<td>(n=165)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>23.8 ± 10.2</td>
<td>24.3 ± 10.5</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>2.1 ± 8.2</td>
<td>-0.7 ± 7.5</td>
<td>3.8 ± 1.4</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td></td>
<td>2.88&lt;sup&gt;1&lt;/sup&gt;</td>
<td>n/a</td>
<td>0.007&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td></td>
<td>&lt;0.001&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT - LOCF population</td>
<td>(n=287)</td>
<td>(n=154)</td>
<td>(n=289)</td>
<td>(n=158)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>24.0 ± 10.3</td>
<td>24.5 ± 10.6</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>2.5 ± 8.4</td>
<td>-0.8 ± 7.5</td>
<td>3.7 ± 1.4</td>
<td>4.3 ± 1.5</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td></td>
<td>3.54&lt;sup&gt;1&lt;/sup&gt;</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td></td>
<td>&lt;0.001&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td>&lt;0.001&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> Based on ANCOVA with treatment and country as factors and baseline ADAS-Cog as a covariate. A positive change indicates improvement.

<sup>2</sup> 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

<table>
<thead>
<tr>
<th>Dementia associated with Parkinson’s Disease</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
<th>ADAS-Cog Exelon</th>
<th>ADAS-Cog Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with visual hallucinations</td>
<td>Patients without visual hallucinations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT + RDO population</td>
<td>(n=107)</td>
<td>(n=60)</td>
<td>(n=220)</td>
<td>(n=101)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>25.4 ± 9.9</td>
<td>27.4 ± 10.4</td>
<td>23.1 ± 10.4</td>
<td>22.5 ± 10.1</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>1.0 ± 9.2</td>
<td>-2.1 ± 8.3</td>
<td>2.6 ± 7.6</td>
<td>0.1 ± 6.9</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>4.27(^1)</td>
<td>2.09(^1)</td>
<td>0.002(^1)</td>
<td>0.015(^1)</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT + RDO population</td>
<td>(n=87)</td>
<td>(n=44)</td>
<td>(n=237)</td>
<td>(n=115)</td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>32.6 ± 10.4</td>
<td>33.7 ± 10.3</td>
<td>20.6 ± 7.9</td>
<td>20.7 ± 7.9</td>
</tr>
<tr>
<td>Mean change at 24 weeks ± SD</td>
<td>2.6 ± 9.4</td>
<td>-1.8 ± 7.2</td>
<td>1.9 ± 7.7</td>
<td>-0.2 ± 7.5</td>
</tr>
<tr>
<td>Adjusted treatment difference</td>
<td>4.73(^1)</td>
<td>2.14(^1)</td>
<td>0.002(^1)</td>
<td>0.010(^1)</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) 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 Exelon 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\(\text{max}\)) by 74 min and lowers C\(\text{max}\) 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 isoenzymes: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, CYP2C19, or CYP2B6. Based on evidence from animal studies the major cytochrome P450 isoenzymes are minimally involved in rivastigmine metabolism. Total plasma clearance of rivastigmine was approximately 130 l/h after a 0.2 mg intravenous dose and decreased to 70 l/h after a 2.7 mg intravenous dose.

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

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

Older people
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
Citric acid
Sodium citrate
Quinoline yellow WS dye (E104)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Exelon 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom
8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/013
EU/1/98/066/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 May 1998
Date of latest renewal: 12 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
Exelon 4.6 mg/24 h transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each transdermal patch releases 4.6 mg of rivastigmine per 24 hours. Each transdermal patch of 5 cm² contains 9 mg of rivastigmine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
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 “Exelon”, “4.6 mg/24 h” and “AMCX”.

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**

<table>
<thead>
<tr>
<th>Transdermal patches</th>
<th>Rivastigmine <em>in vivo</em> release rates per 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exelon 4.6 mg/24 h</td>
<td>4.6 mg</td>
</tr>
<tr>
<td>Exelon 9.5 mg/24 h</td>
<td>9.5 mg</td>
</tr>
<tr>
<td>Exelon 13.3 mg/24 h</td>
<td>13.3 mg</td>
</tr>
</tbody>
</table>

**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 Exelon capsules or oral solution can be switched to Exelon 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 Exelon 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

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

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

4.4 Special warnings and precautions for use

The incidence and severity of adverse reactions generally increase with 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 Exelon 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 Exelon 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 Exelon transdermal patches.

Bradycardia

Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).
Other adverse reactions
Care must be taken when prescribing Exelon 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 Exelon 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 Exelon 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 torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sulotropride, amisulpride, tiapride, veralipride), pimozone, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacin should be observed with caution and clinical monitoring (ECG) may also be required.

No pharmacokinetic interaction was observed between 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 Exelon 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 Exelon transdermal patches for a duration of 24-48 weeks and from post-marketing data.

Table 1

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Urinary tract infection</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Anorexia, decreased appetite</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dehydration</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Anxiety, depression, delirium, agitation</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Aggression</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Hallucinations, restlessness, nightmares</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Headache, syncope, dizziness</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Psychomotor hyperactivity</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Extrapyramidal symptoms</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Worsening of Parkinson’s disease, seizure, tremor, somnolence</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Bradycardia</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Atrioventricular block, atrial fibrillation, tachycardia, sick sinus syndrome</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vascular disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Hypertension</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Gastric ulcer</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Pancreatitis</td>
<td></td>
</tr>
</tbody>
</table>
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 Exelon 13.3 mg/24 h transdermal patches than with placebo.

The following adverse reactions have only been observed with Exelon capsules and oral solution and not in clinical studies with Exelon 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 Exelon 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 Exelon 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 Exelon 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.

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

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

* 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**

<table>
<thead>
<tr>
<th>ITT-LOCF population</th>
<th>Patients with clinically significant response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exelon transdermal patches 9.5 mg/24 h N = 251</td>
</tr>
<tr>
<td>At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL</td>
<td>17.4</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>0.037*</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Population/Visit</th>
<th>Exelon 15 cm² N = 265</th>
<th>Exelon 10 cm² N = 271</th>
<th>Exelon 15 cm²</th>
<th>Exelon 10 cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean</td>
<td>n</td>
<td>Mean</td>
</tr>
<tr>
<td>ADAS-Cog LOCF</td>
<td>264</td>
<td>34.4</td>
<td>268</td>
<td>34.9</td>
</tr>
<tr>
<td>DB-week 48 Value</td>
<td>264</td>
<td>38.5</td>
<td>268</td>
<td>39.7</td>
</tr>
<tr>
<td>Change</td>
<td>264</td>
<td>4.1</td>
<td>268</td>
<td>-0.8</td>
</tr>
<tr>
<td>ADCS-IADL LOCF</td>
<td>265</td>
<td>27.5</td>
<td>271</td>
<td>25.8</td>
</tr>
<tr>
<td>Week 48 Value</td>
<td>265</td>
<td>23.1</td>
<td>271</td>
<td>19.6</td>
</tr>
<tr>
<td>Change</td>
<td>265</td>
<td>-4.4</td>
<td>271</td>
<td>-6.2</td>
</tr>
</tbody>
</table>

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 Exelon 15 cm² as compared to Exelon 10 cm².
ADCS-IADL scores: A positive difference in DLSM indicates greater improvement in Exelon 15 cm² as compared to Exelon 10 cm².
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 Exelon 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 Exelon transdermal patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5-1 hour. Cmax 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 ($C_{\text{max}}$ 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 ($((C_{\text{max}} - C_{\text{min}})/C_{\text{avg}})$, was 0.58 for Exelon 4.6 mg/24 h transdermal patches, 0.77 for Exelon 9.5 mg/24 h transdermal patches and 0.72 for Exelon 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% ($C_{\text{max}}$) 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% ($C_{\text{max}}$) 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$_\infty$) 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 $t_{1/2}$ 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 isozenzymes 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$_{\infty}$ 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.

**Older people**

Age had no impact on the exposure to rivastigmine in Alzheimer’s disease patients treated with Exelon transdermal patches.

**Hepatic impairment**

No study was conducted with Exelon transdermal patches in subjects with hepatic impairment. After oral administration, the C$_{\text{max}}$ 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 Exelon 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 Exelon 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

Each child-resistant sachet is made of a paper/polyester/aluminium/polyacrylonitrile multilaminated material. One sachet contains one transdermal patch.

Available in packs containing 7, 30 or 42 sachets and in multipacks containing 60, 84 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. **MARKETING AUTHORISATION NUMBERS**

EU/1/98/066/019-022
EU/1/98/066/031-032

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 12 May 1998
Date of latest renewal: 12 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**

Exelon 9.5 mg/24 h transdermal patch

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

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

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

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 “Exelon”, “9.5 mg/24 h” and “BHDI”.

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**

<table>
<thead>
<tr>
<th>Transdermal patches</th>
<th>Rivastigmine in vivo release rates per 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exelon 4.6 mg/24 h</td>
<td>4.6 mg</td>
</tr>
<tr>
<td>Exelon 9.5 mg/24 h</td>
<td>9.5 mg</td>
</tr>
<tr>
<td>Exelon 13.3 mg/24 h</td>
<td>13.3 mg</td>
</tr>
</tbody>
</table>

**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 Exelon capsules or oral solution can be switched to Exelon 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 Exelon 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

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

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

4.4 Special warnings and precautions for use

The incidence and severity of adverse reactions generally increase with 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 Exelon 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 Exelon 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 Exelon transdermal patches.

Bradycardia

Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).
Other adverse reactions
Care must be taken when prescribing Exelon 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 Exelon 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 Exelon 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 or other bradycardia agents (e.g. class III antiarrhythmic agents, calcium channel antagonists, digitalis glycoside, pilocarpin).

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

No pharmacokinetic interaction was observed between 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, anti-diabetics, 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 Exelon 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 Exelon transdermal patches for a duration of 24-48 weeks and from post-marketing data.

Table 1

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Common</th>
<th>Urinary tract infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Anorexia, decreased appetite</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Dehydration</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Anxiety, depression, delirium, agitation</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Aggression</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Hallucinations, restlessness, nightmares</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache, syncope, dizziness</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Psychomotor hyperactivity</td>
<td></td>
</tr>
<tr>
<td>Very rare</td>
<td>Extrapyramidal symptoms</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Worsening of Parkinson’s disease, seizure, tremor, somnolence</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Not known</td>
<td>Atrioventricular block, atrial fibrillation, tachycardia, sick sinus syndrome</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Not known</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Gastric ulcer</td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known</td>
<td>Hepatitis, elevated liver function tests</td>
</tr>
</tbody>
</table>
**Skin and subcutaneous tissue disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Rash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not known</td>
<td>Pruritus, erythema, urticaria, vesicles, allergic dermatitis (disseminated)</td>
</tr>
</tbody>
</table>

**Renal and urinary disorders**

<table>
<thead>
<tr>
<th>Common</th>
<th>Urinary incontinence</th>
</tr>
</thead>
</table>

**General disorders and administration site conditions**

<table>
<thead>
<tr>
<th>Common</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Fall</td>
</tr>
</tbody>
</table>

*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 Exelon 13.3 mg/24 h transdermal patches than with placebo.

The following adverse reactions have only been observed with Exelon capsules and oral solution and not in clinical studies with Exelon 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 Exelon 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 Exelon 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 Exelon 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.

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

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

* 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

<table>
<thead>
<tr>
<th>ITT-LOCF population</th>
<th>Patients with clinically significant response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exelon transdermal patches 9.5 mg/24 h N = 251</td>
</tr>
<tr>
<td>At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL</td>
<td>17.4</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>0.037*</td>
</tr>
</tbody>
</table>

*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.
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

<table>
<thead>
<tr>
<th>Population/Visit</th>
<th>Exelon 15 cm² (N = 265)</th>
<th>Exelon 10 cm² (N = 271)</th>
<th>Exelon 15 cm²</th>
<th>Exelon 10 cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (Mean)</td>
<td>n (Mean)</td>
<td>DLSM 95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>ADAS-Cog</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOCF Baseline</td>
<td>264 (34.4)</td>
<td>268 (34.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DB-week 48 Value</td>
<td>264 (38.5)</td>
<td>268 (39.7)</td>
<td>-0.8 (-2.1, 0.5)</td>
<td>0.227</td>
</tr>
<tr>
<td>ADCS-IADL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOCF Baseline</td>
<td>265 (27.5)</td>
<td>271 (25.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48 Value</td>
<td>265 (23.1)</td>
<td>271 (19.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change</td>
<td>265 (-4.4)</td>
<td>271 (-6.2)</td>
<td>2.2 (0.8, 3.6)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

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 Exelon 15 cm² as compared to Exelon 10 cm².  
ADCS-IADL scores: A positive difference in DLSM indicates greater improvement in Exelon 15 cm² as compared to Exelon 10 cm².  
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 Exelon 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 Exelon transdermal patches is slow. After the first dose, detectable plasma concentrations are observed after a lag time of 0.5-1 hour. C<sub>max</sub> 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 \((C_{\text{max}}\text{ and AUC})\) 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 \(((C_{\text{max}}-C_{\text{min}})/C_{\text{avg}})\), was 0.58 for Exelon 4.6 mg/24 h transdermal patches, 0.77 for Exelon 9.5 mg/24 h transdermal patches and 0.72 for Exelon 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% \((C_{\text{max}})\) and 49% \((\text{AUC}_{0-24h})\) 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% \((C_{\text{max}})\) and 43% \((\text{AUC}_{0-24h})\) 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 \((\text{AUC}_{\infty})\) 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 \(t_{\text{1/2}}\) 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 14C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces.

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.

**Older people**

Age had no impact on the exposure to rivastigmine in Alzheimer’s disease patients treated with Exelon transdermal patches.

**Hepatic impairment**

No study was conducted with Exelon transdermal patches in subjects with hepatic impairment. After oral administration, the Cmax of rivastigmine was approximately 60% higher and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects.

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 Exelon 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 10⁴ 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 Exelon 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

Back 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

Each child-resistant sachet is made of a paper/polyester/aluminium/polyacrylonitrile multilaminated material. One sachet contains one transdermal patch.

Available in packs containing 7, 30 or 42 sachets and in multipacks containing 60, 84 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/98/066/023-026
EU/1/98/066/033-034

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 May 1998
Date of latest renewal: 12 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**

Exelon 13.3 mg/24 h transdermal patch

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each transdermal patch releases 13.3 mg of rivastigmine per 24 hours. Each transdermal patch of 15 cm² contains 27 mg of rivastigmine.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

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 “Exelon”, “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**

<table>
<thead>
<tr>
<th>Transdermal patches</th>
<th>Rivastigmine <em>in vivo</em> release rates per 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exelon 4.6 mg/24 h</td>
<td>4.6 mg</td>
</tr>
<tr>
<td>Exelon 9.5 mg/24 h</td>
<td>9.5 mg</td>
</tr>
<tr>
<td>Exelon 13.3 mg/24 h</td>
<td>13.3 mg</td>
</tr>
</tbody>
</table>

**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 Exelon capsules or oral solution can be switched to Exelon 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 Exelon 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

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

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

4.4 Special warnings and precautions for use

The incidence and severity of adverse reactions generally increase with 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 Exelon 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 Exelon 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 Exelon transdermal patches.

Bradycardia

Rivastigmine may cause bradycardia which constitutes a risk factor in the occurrence of torsade de pointes, predominantly in patients with risk factors. Caution is advised in patients at higher risk of developing torsade de pointes; for example, those with uncompensated heart failure, recent myocardial infarction, bradyarrhythmias, a predisposition to hypokalaemia or hypomagnesaemia, or concomitant use with medicinal products known to induce QT prolongation and/or torsade de pointes (see sections 4.5 and 4.8).
Other adverse reactions
Care must be taken when prescribing Exelon 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 Exelon 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 Exelon 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 torsades de pointes-inducing medicinal products such as antipsychotics i.e. some phenothiazines (chlorpromazine, levomepromazine), benzamides (sulpiride, sulotropride, amisulpride, tiapride, veralipride), pimozide, haloperidol, droperidol, cisapride, citalopram, diphemanil, erythromycin IV, halofantrin, mizolastin, methadone, pentamidine and moxifloxacin should be observed with caution and clinical monitoring (ECG) may also be required.

No pharmacokinetic interaction was observed between 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 Exelon 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 Exelon transdermal patches for a duration of 24-48 weeks and from post-marketing data.

Table 1

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>Common</th>
<th>Urinary tract infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Common</td>
<td>Anorexia, decreased appetite</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Common</td>
<td>Anxiety, depression, delirium, agitation</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Aggression</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Hallucinations, restlessness, nightmares</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache, syncope, dizziness</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Psychomotor hyperactivity</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td>Extrapyramidal symptoms</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Worsening of Parkinson’s disease, seizure, tremor, somnolence</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Atrioventricular block, atrial fibrillation, tachycardia, sick sinus syndrome</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Not known</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea, vomiting, diarrhoea, dyspepsia, abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Gastric ulcer</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td><strong>Hepatobiliary disorders</strong></td>
<td>Not known</td>
<td>Hepatitis, elevated liver function tests</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Common</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Pruritus, erythema, urticaria, vesicles, allergic dermatitis (disseminated)</td>
</tr>
<tr>
<td><strong>Renal and urinary disorders</strong></td>
<td>Common</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td>Common</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Fall</td>
</tr>
</tbody>
</table>

*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 Exelon 13.3 mg/24 h transdermal patches than with placebo.

The following adverse reactions have only been observed with Exelon capsules and oral solution and not in clinical studies with Exelon 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 Exelon 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 Exelon 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 Exelon 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.

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

<table>
<thead>
<tr>
<th>ITT-LOCF population</th>
<th>Exelon transdermal patches 9.5 mg/24 h N = 251</th>
<th>Exelon capsules 12 mg/day N = 256</th>
<th>Placebo N = 282</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAS-Cog</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>(n=248)</td>
<td>(n=253)</td>
<td>(n=281)</td>
</tr>
<tr>
<td>Mean change at week 24 ± SD</td>
<td>-0.6 ± 6.4</td>
<td>-0.6 ± 6.2</td>
<td>1.0 ± 6.8</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>0.005*¹</td>
<td>0.003*¹</td>
<td></td>
</tr>
<tr>
<td>ADCS-CGIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean score ± SD</td>
<td>(n=248)</td>
<td>(n=253)</td>
<td>(n=278)</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>0.010*²</td>
<td>0.009*²</td>
<td></td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline ± SD</td>
<td>(n=247)</td>
<td>(n=254)</td>
<td>(n=281)</td>
</tr>
<tr>
<td>Mean change at week 24 ± SD</td>
<td>-0.1 ± 9.1</td>
<td>-0.5 ± 9.5</td>
<td>-2.3 ± 9.4</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>0.013*¹</td>
<td>0.039*¹</td>
<td></td>
</tr>
</tbody>
</table>

* 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

<table>
<thead>
<tr>
<th>ITT-LOCF population</th>
<th>Patients with clinically significant response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exelon transdermal patches 9.5 mg/24 h N = 251</td>
</tr>
<tr>
<td>At least 4 points improvement on ADAS-Cog with no worsening on ADCS-CGIC and ADCS-ADL</td>
<td>17.4</td>
</tr>
<tr>
<td>p-value versus placebo</td>
<td>0.037*</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Population/Visit</th>
<th>Exelon 15 cm²</th>
<th>Exelon 10 cm²</th>
<th>Exelon 15 cm²</th>
<th>Exelon 10 cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 265</td>
<td>n = 271</td>
<td>n = 265</td>
<td>n = 271</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>Mean</td>
<td>DLSM</td>
<td>95% CI</td>
</tr>
<tr>
<td>ADAS-Cog</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOCF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>264</td>
<td>34.4</td>
<td>268</td>
<td>34.9</td>
</tr>
<tr>
<td>DB-week 48 Value</td>
<td>264</td>
<td>38.5</td>
<td>268</td>
<td>39.7</td>
</tr>
<tr>
<td>Change</td>
<td>264</td>
<td>4.1</td>
<td>268</td>
<td>4.9</td>
</tr>
<tr>
<td>ADCS-IADL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOCF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>265</td>
<td>27.5</td>
<td>271</td>
<td>25.8</td>
</tr>
<tr>
<td>Week 48 Value</td>
<td>265</td>
<td>23.1</td>
<td>271</td>
<td>19.6</td>
</tr>
<tr>
<td>Change</td>
<td>265</td>
<td>-4.4</td>
<td>271</td>
<td>-6.2</td>
</tr>
</tbody>
</table>

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 Exelon 15 cm² as compared to Exelon 10 cm².
ADCS-IADL scores: A positive difference in DLSM indicates greater improvement in Exelon 15 cm² as compared to Exelon 10 cm².
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 Exelon 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 Exelon 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 ($C_{\text{max}}$ 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 ($\frac{(C_{\text{max}}-C_{\text{min}})}{C_{\text{avg}}}$), was 0.58 for Exelon 4.6 mg/24 h transdermal patches, 0.77 for Exelon 9.5 mg/24 h transdermal patches and 0.72 for Exelon 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% ($C_{\text{max}}$) and 49% (AUC$_{0-24\text{h}}$) 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% ($C_{\text{max}}$) and 43% (AUC$_{0-24\text{h}}$) 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$_{\infty}$) 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 $t_{\text{1/2}}$ 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 14C-rivastigmine, renal elimination was rapid and essentially complete (>90%) within 24 hours. Less than 1% of the administered dose is excreted in the faeces.

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.

**Older people**

Age had no impact on the exposure to rivastigmine in Alzheimer’s disease patients treated with Exelon transdermal patches.

**Hepatic impairment**

No study was conducted with Exelon transdermal patches in subjects with hepatic impairment. After oral administration, the Cmax of rivastigmine was approximately 60% higher and the AUC of rivastigmine was more than twice as high in subjects with mild to moderate hepatic impairment than in healthy subjects.

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 Exelon 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 10⁶ 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 Exelon 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

Each child-resistant sachet is made of a paper/polyester/aluminium/polyacrylonitrile multilaminated material. One sachet contains one transdermal patch.

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/027-030

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 May 1998
Date of latest renewal: 12 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.
Planta de Producción
Ronda de Santa Maria 158
E-08210 Barberà del Vallès, Barcelona
Spain

**Oral solution**
Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

**Transdermal patch**
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**
The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

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

- 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 Exelon patch is marketed, all physicians who are expected to prescribe Exelon 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

Exelon 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

<table>
<thead>
<tr>
<th>Number</th>
<th>Pack Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU/1/98/066/001</td>
<td>28 hard capsules</td>
</tr>
<tr>
<td>EU/1/98/066/002</td>
<td>56 hard capsules</td>
</tr>
<tr>
<td>EU/1/98/066/003</td>
<td>112 hard capsules</td>
</tr>
</tbody>
</table>

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 1.5 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Exelon 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 AND THE IMMEDIATE PACKAGING

**BOTTLE LABEL**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exelon 1.5 mg hard capsules rivastigmine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 capsule contains 1.5 mg rivastigmine present as rivastigmine hydrogen tartrate.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 hard capsules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use. Oral use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>To be swallowed whole without crushing or opening.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not store above 30°C.</td>
</tr>
</tbody>
</table>
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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/066/014

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Exelon 1.5 mg
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLDING BOX</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1. NAME OF THE MEDICINAL PRODUCT</td>
</tr>
<tr>
<td>Exelon 3.0 mg hard capsules</td>
</tr>
<tr>
<td>rivastigmine</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2. STATEMENT OF ACTIVE SUBSTANCE(S)</td>
</tr>
<tr>
<td>1 capsule contains 3.0 mg rivastigmine present as rivastigmine hydrogen tarrate.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3. LIST OF EXCIPIENTS</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>4. PHARMACEUTICAL FORM AND CONTENTS</td>
</tr>
<tr>
<td>28 hard capsules</td>
</tr>
<tr>
<td>56 hard capsules</td>
</tr>
<tr>
<td>112 hard capsules</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>5. METHOD AND ROUTE(S) OF ADMINISTRATION</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</td>
</tr>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>7. OTHER SPECIAL WARNING(S), IF NECESSARY</td>
</tr>
<tr>
<td>To be swallowed whole without crushing or opening.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>8. EXPIRY DATE</td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>9. SPECIAL STORAGE CONDITIONS</td>
</tr>
<tr>
<td>Do not store above 30°C.</td>
</tr>
</tbody>
</table>
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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/004  28 hard capsules
EU/1/98/066/005  56 hard capsules
EU/1/98/066/006  112 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 3.0 mg
### Minimum Particulars to Appear on Blisters or Strips

#### Blisters

<table>
<thead>
<tr>
<th>1. Name of the Medicinal Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exelon 3.0 mg hard capsules rivastigmine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Name of the Marketing Authorisation Holder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis Europharm Limited</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>3. Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Batch Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
</tr>
<tr>
<td>Tuesday</td>
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<tr>
<td>Wednesday</td>
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<tr>
<td>Thursday</td>
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<tr>
<td>Friday</td>
</tr>
<tr>
<td>Saturday</td>
</tr>
<tr>
<td>Sunday</td>
</tr>
</tbody>
</table>
1. NAME OF THE MEDICINAL PRODUCT

Exelon 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

250 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be swallowed whole without crushing or opening.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 3.0 mg
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLDING BOX</td>
</tr>
</tbody>
</table>

### 1. NAME OF THE MEDICINAL PRODUCT

Exelon 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/007  28 hard capsules
EU/1/98/066/008  56 hard capsules
EU/1/98/066/009  112 hard capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 4.5 mg
MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. **NAME OF THE MEDICINAL PRODUCT**

   Exelon 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
<p>| PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING |</p>
<table>
<thead>
<tr>
<th>BOTTLE LABEL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Exelon 4.5 mg hard capsules</td>
</tr>
<tr>
<td>rivastigmine</td>
</tr>
<tr>
<td><strong>2. STATEMENT OF ACTIVE SUBSTANCE(S)</strong></td>
</tr>
<tr>
<td>1 capsule contains 4.5 mg rivastigmine present as rivastigmine hydrogen tartrate.</td>
</tr>
<tr>
<td><strong>3. LIST OF EXCIPIENTS</strong></td>
</tr>
<tr>
<td><strong>4. PHARMACEUTICAL FORM AND CONTENTS</strong></td>
</tr>
<tr>
<td>250 hard capsules</td>
</tr>
<tr>
<td><strong>5. METHOD AND ROUTE(S) OF ADMINISTRATION</strong></td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>Oral use.</td>
</tr>
<tr>
<td><strong>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</strong></td>
</tr>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
<tr>
<td><strong>7. OTHER SPECIAL WARNING(S), IF NECESSARY</strong></td>
</tr>
<tr>
<td>To be swallowed whole without crushing or opening.</td>
</tr>
<tr>
<td><strong>8. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td><strong>9. SPECIAL STORAGE CONDITIONS</strong></td>
</tr>
<tr>
<td>Do not store above 30°C.</td>
</tr>
</tbody>
</table>
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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORIZATION NUMBER(S)

EU/1/98/066/016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 4.5 mg
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

FOLDING BOX

1. NAME OF THE MEDICINAL PRODUCT

Exelon 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 AUTHORIZATION HOLDER**

Novartis Europharm Limited  
Frimley Business Park  
Camberley GU16 7SR  
United Kingdom

12. **MARKETING AUTHORIZATION NUMBER(S)**

- EU/1/98/066/010  
  28 hard capsules
- EU/1/98/066/011  
  56 hard capsules
- EU/1/98/066/012  
  112 hard capsules

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Exelon 6.0 mg
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLISTERS</td>
</tr>
<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT</strong></td>
</tr>
<tr>
<td>Exelon 6.0 mg hard capsules</td>
</tr>
<tr>
<td>rivastigmine</td>
</tr>
<tr>
<td><strong>2. NAME OF THE MARKETING AUTHORISATION HOLDER</strong></td>
</tr>
<tr>
<td>Novartis Europharm Limited</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
</tr>
<tr>
<td>EXP</td>
</tr>
<tr>
<td><strong>4. BATCH NUMBER</strong></td>
</tr>
<tr>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. OTHER</strong></td>
</tr>
<tr>
<td>Monday</td>
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<tr>
<td>Tuesday</td>
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<tr>
<td>Wednesday</td>
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<td>Thursday</td>
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<td>Friday</td>
</tr>
<tr>
<td>Saturday</td>
</tr>
<tr>
<td>Sunday</td>
</tr>
</tbody>
</table>
### 1. NAME OF THE MEDICINAL PRODUCT

Exelon 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

250 hard capsules

### 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

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

Keep out of the sight and reach of children.

### 7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be swallowed whole without crushing or opening.

### 8. EXPIRY DATE

EXP

### 9. SPECIAL STORAGE CONDITIONS

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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/017

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 6.0 mg
1. **NAME OF THE MEDICINAL PRODUCT**

Exelon 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, 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 Exelon 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/018  50 ml
EU/1/98/066/013  120 ml

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 2 mg/ml [folding box only]
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Exelon 4.6 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 5 cm² 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
42 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 AUTHORIZATION HOLDER**

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. **MARKETING AUTHORIZATION NUMBER(S)**

<table>
<thead>
<tr>
<th>Number</th>
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</thead>
<tbody>
<tr>
<td>EU/1/98/066/019</td>
<td>7 transdermal patches</td>
</tr>
<tr>
<td>EU/1/98/066/020</td>
<td>30 transdermal patches</td>
</tr>
<tr>
<td>EU/1/98/066/031</td>
<td>42 transdermal patches</td>
</tr>
</tbody>
</table>

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Exelon 4.6 mg/24 h
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Exelon 4.6 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 5 cm² 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.
42 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/98/066/021  60 transdermal patches
EU/1/98/066/022  90 transdermal patches
EU/1/98/066/032  84 transdermal patches

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 4.6 mg/24 h
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Exelon 4.6 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 5 cm² 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
Multipack: 84 (2 packs of 42) 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

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13. BATCH NUMBER

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14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 4.6 mg/24 h
1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Exelon 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

Exelon 9.5 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 10 cm² 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
42 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**

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15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Exelon 9.5 mg/24 h
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
INTERMEDIATE CARTON OF MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT
Exelon 9.5 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)
1 transdermal patch of 10 cm² 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.
42 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

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13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 9.5 mg/24 h
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

Exelon 9.5 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 10 cm² 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
Multipack: 84 (2 packs of 42) 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

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15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Exelon 9.5 mg/24 h
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<tr>
<td>Exelon 9.5 mg/24 h transdermal patch</td>
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<tr>
<td>rivastigmine</td>
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<tr>
<td><strong>2. METHOD OF ADMINISTRATION</strong></td>
</tr>
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<td>Read the package leaflet before use.</td>
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<tr>
<td>Transdermal use</td>
</tr>
<tr>
<td><strong>3. EXPIRY DATE</strong></td>
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<tr>
<td>Lot</td>
</tr>
<tr>
<td><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
</tr>
<tr>
<td>1 transdermal patch per sachet</td>
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<tr>
<td><strong>6. OTHER</strong></td>
</tr>
<tr>
<td>Apply one patch per day. Take off the previous patch before putting ONE new patch on.</td>
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</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON FOR UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Exelon 13.3 mg/24 h transdermal patch
rivastigmine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 transdermal patch of 15 cm² 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/066/027  7 transdermal patches
EU/1/98/066/028  30 transdermal patches

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Exelon 13.3 mg/24 h
1. NAME OF THE MEDICINAL PRODUCT
Exelon 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
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/98/066/0692 60 transdermal patches
EU/1/98/066/030 90 transdermal patches

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Exelon 13.3 mg/24 h
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (WITH BLUE BOX)

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<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
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<td>Multipack: 60 (2 packs of 30) transdermal patches</td>
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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
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United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

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EU/1/98/066/030  90 transdermal patches

13. **BATCH NUMBER**

Lot

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Exelon 13.3 mg/24 h
**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**SACHET**

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

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

1. What Exelon is and what it is used for

The active substance of Exelon 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, Exelon 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.

Exelon 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 Exelon

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

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

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

If you have not taken Exelon 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 Exelon in the paediatric population in the treatment of Alzheimer’s disease.

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

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

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

Caution when Exelon is taken together with beta-blockers (medicines such as atenolol used to treat hypertension, angina and other heart conditions). Taking the two medicines together could cause problems such as slowing of the heartbeat (bradycardia) leading to fainting or loss of consciousness.
**Pregnancy, breast-feeding and fertility**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

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

You should not breast-feed during treatment with Exelon.

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

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

- 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 Exelon 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 Exelon 1.5 mg capsule contains 1.5 mg of rivastigmine.
Each Exelon 3.0 mg capsule contains 3.0 mg of rivastigmine.
Each Exelon 4.5 mg capsule contains 4.5 mg of rivastigmine.
Each Exelon 6.0 mg capsule contains 6.0 mg of rivastigmine.

**What Exelon looks like and contents of the pack**

- Exelon 1.5 mg hard capsules, which contain an off-white to slightly yellow powder, have a yellow cap and yellow body, with red imprint “EXELON 1.5 mg” on the body.
- Exelon 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 “EXELON 3 mg” on the body.
- Exelon 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 “EXELON 4.5 mg” on the body.
- Exelon 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 “EXELON 6 mg” on the body.

They are packed in blisters available in three different pack sizes (28, 56 or 112 capsules) and plastic bottles of 250 capsules, but these may not all be available in your country.

**Marketing Authorisation holder**

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

**Manufacturer**

Novartis Farmacéutica, S.A.
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Spain
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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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
Exelon 2 mg/ml oral solution
rivastigmine

Package leaflet: Information for the user

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

1. What Exelon is and what it is used for

The active substance of Exelon 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, Exelon 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.

Exelon 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 Exelon

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

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

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

If you have not taken Exelon 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 Exelon in the paediatric population in the treatment of Alzheimer’s disease.

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

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

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

Caution when Exelon is taken together with beta-blockers (medicines such as atenolol used to treat hypertension, angina, and other heart conditions). Taking the two medicines together could cause problems such as slowing of the heartbeat (bradycardia) leading to fainting or loss of consciousness.
Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

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

You should not breast-feed during treatment with Exelon.

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

Important information about some of the ingredients of Exelon
One of the inactive ingredients in Exelon oral solution is sodium benzoate. Benzoic acid is a mild irritant to the skin, eyes and mucous membranes.

3. How to take Exelon

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 Exelon 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 Exelon 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 Exelon.
- To benefit from your medicine, take it every day.
- Take Exelon 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 Exelon than you should
If you accidentally take more Exelon than you should, inform your doctor. You may require medical attention. Some people who have accidentally taken too much Exelon 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 Exelon
If you find you have forgotten to take your dose of Exelon, 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 Exelon 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 Exelon
- 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 Exelon 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 Exelon 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, citric acid, sodium citrate, quinoline yellow WS dye (E104) and purified water.

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

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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

Exelon 4.6 mg/24 h transdermal patch
Exelon 9.5 mg/24 h transdermal patch
Exelon 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 Exelon is and what it is used for
2. What you need to know before you use Exelon
3. How to use Exelon
4. Possible side effects
5. How to store Exelon
6. Contents of the pack and other information

1. What Exelon is and what it is used for

The active substance of Exelon 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, Exelon allows levels of acetylcholine to be increased in the brain, helping to reduce the symptoms of Alzheimer’s disease.

Exelon 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 Exelon

Do not use Exelon
- if you are allergic to rivastigmine (the active substance in Exelon) 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 Exelon transdermal patches.
**Warnings and precautions**

Talk to your doctor before using Exelon:
- if you have, or have ever had, an irregular or slow heartbeat.
- if you have, or have ever had, an active stomach ulcer.
- if you have, or have ever had, difficulties in passing urine.
- if you have, or have ever had, seizures.
- if you have, or have ever had, asthma or 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 Exelon in the paediatric population in the treatment of Alzheimer’s disease.

**Other medicines and Exelon**

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

Exelon 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).

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

Caution when Exelon 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.

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

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

**Driving and using machines**

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

Always use Exelon 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 Exelon transdermal patch is most suitable for you.
- Treatment usually starts with Exelon 4.6 mg/24 h.
- The recommended usual daily dose is Exelon 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 Exelon 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 Exelon 4.6 mg/24 h.

Exelon can be used with food, drink and alcohol.

Where to apply your Exelon 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 Exelon transdermal patch**

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

**If you use more Exelon 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 Exelon 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 Exelon**
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 Exelon
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, Exelon 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 Exelon 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 Exelon**
- 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. If your community burns domestic rubbish, you can dispose of the patch with your domestic rubbish. Otherwise, return used patches to a pharmacy, preferably in the original packaging.
6. Contents of the pack and other information

What Exelon contains
- The active substance is rivastigmine.
  - Exelon 4.6 mg/24 h transdermal patches: Each patch releasing 4.6 mg of rivastigmine per 24 hours is 5 cm² and contains 9 mg of rivastigmine.
  - Exelon 9.5 mg/24 h transdermal patches: Each patch releasing 9.5 mg of rivastigmine per 24 hours is 10 cm² and contains 18 mg of rivastigmine.
  - Exelon 13.3 mg/24 h transdermal patches: Each patch releasing 13.3 mg of rivastigmine per 24 hours is 15 cm² 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 Exelon 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:
- “Exelon”, “4.6 mg/24 h” and “AMCX”,
- “Exelon”, “9.5 mg/24 h” and “BHDI”,
- “Exelon”, “13.3 mg/24 h” and “CNFU”.

One transdermal patch is sealed in one sachet. Exelon 4.6 mg/24 h transdermal patches and Exelon 9.5 mg/24 h transdermal patches are available in packs containing 7, 30 or 42 sachets and in multipacks containing 60, 84 or 90 sachets. Exelon 13.3 mg/24 h transdermal 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.

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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
ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS RECOMMENDING THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION
Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for rivastigmine, the scientific conclusions of CHMP are as follows:

- **Cardiac arrhythmia**

Cardiac arrhythmia / bradycardia are listed adverse reactions for rivastigmine.

During the reporting period, 2 cases of torsade de pointe have been reported. Of these 2 cases of torsade de pointes with positive dechallenge after dose reduction or discontinuation of rivastigmine, the causal role of rivastigmine due to its bradycardia-related adverse event could not be ruled out despite the confounding factors in these cases (venlafaxine, tiapride).

Rivastigmine is known to induce bradycardia which constitutes a risk factor of QT prolongation and post-marketing cases of cardiac arrhythmia have been reported with the use of rivastigmine, especially in patients with other risk factors for QTc prolongation / Torsade de pointes (TdP) (concomitant treatments known to induce TdP, relevant cardiac disorders).

- **Nightmares**

During the reporting period 35 cases of nightmares were reported and 324 cumulatively (124 with oral formulations, 176 with patch formulations, 16 with unknown formulation and 4 with oral plus patch formulation). 26 relevant cases with positive dechallenge after discontinuation or dose reduction or positive rechallenge were identified. When documented the temporal relationship between the event onset and the start of rivastigmine indicates a causal relationship.

Due to the scientific literature, the significant proportional reporting ratio (PRR) for nightmares in EudraVigilance, data from clinical trials with oral formulation and post-marketing cases with both formulations, the PRAC agreed to add “nightmares” as adverse reaction in section 4.8 of the SmPC with frequency “not known” for the patch formulation and frequency “common” for oral formulations of rivastigmine-containing medicines.

Therefore, in view of available data regarding cardiac arrhythmia and nightmares, the PRAC considered that changes to the product information were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for rivastigmine the CHMP is of the opinion that the benefit-risk balance of the medicinal products containing rivastigmine is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisations should be varied.