Public Assessment Report

Decentralised Procedure

DONEPEZIL 5 MG AND 10 MG ORODISPERIBLE TABLETS

DONEPEZIL HYDROCHLORIDE

UK/H/4588/001-2/DC

UK Licence No: PL 10555/0036-7

EISAI LIMITED
DONEPEZIL 5 MG AND 10 MG ORODISPERSIBLE TABLETS
PL 10555/0036-7

LAY SUMMARY

On 20\textsuperscript{th} April 2011, the UK granted Eisai Limited Marketing Authorisations (licences) for Donepezil 5 mg and 10 mg orodispersible tablets (PL 10555/0036-7; UK/H/4588/001-2/DC).

Donepezil 5 mg and 10 mg orodispersible tablets contain the active ingredient, donepezil hydrochloride. Donepezil hydrochloride belongs to a group of medicines called acetylcholinesterase inhibitors.

Donepezil increases the levels of a substance (acetylcholine) in the brain involved in memory function by slowing down the breakdown of acetylcholine. It is used to treat the symptoms of dementia in people diagnosed as having mild and moderately severe Alzheimer’s disease. The symptoms include increasing memory loss, confusion and behavioural changes. As a result, sufferers of Alzheimer’s disease find it more and more difficult to carry out their normal daily activities.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Donepezil 5 mg and 10 mg orodispersible tablets outweigh the risks; hence these Marketing Authorisations have been granted.
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Module 1

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Donepezil 5 mg and 10 mg orodispersible tablets</th>
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<tr>
<td>Type of Application</td>
<td>Simple application, Article 10c</td>
</tr>
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<td>Active Substance</td>
<td>Donepezil hydrochloride</td>
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<tr>
<td>Form</td>
<td>Orodispersible tablets</td>
</tr>
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<td>Strength</td>
<td>5 mg and 10 mg</td>
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<tr>
<td>MA Holder</td>
<td>Eisai Ltd.</td>
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<tr>
<td></td>
<td>European Knowledge Centre</td>
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<td></td>
<td>Mosquito Way, Hatfield</td>
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<td>Herts</td>
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<td>AL10 9SN</td>
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<td></td>
<td>United Kingdom.</td>
</tr>
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<td>Reference Member State (RMS)</td>
<td>UK</td>
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<tr>
<td>Concerned Member States (CMS)</td>
<td>Austria (AT), Belgium (BE), Germany (DE), Denmark (DK), Greece (EL), France (FR), Ireland (IE), Italy (IT), Luxembourg (LU), Portugal (PT), Sweden (SE)</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/4588/001-2/DC</td>
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<tr>
<td>End of Procedure</td>
<td>Day 150 – 29\textsuperscript{th} March 2011</td>
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</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
DONEPEZIL 5 mg orodispersible tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each orodispersible tablet contains 5 mg donepezil hydrochloride, equivalent to 4.56 mg of donepezil free base.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Orodispersible tablet.
White orodispersible tablet embossed with “5” on one side.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
DONEPEZIL orodispersible tablets are indicated for the symptomatic treatment of:
- mild to moderately severe Alzheimer’s dementia

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Adults/Elderly:
Treatment is initiated at 5 mg/day (once-a-day dosing). DONEPEZIL should be taken orally, in the evening, just prior to retiring. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference. The 5 mg/day dose should be maintained for at least one month in order to allow the earliest clinical responses to treatment to be assessed and to allow steady-state concentrations of donepezil hydrochloride to be achieved. Following a one-month clinical assessment of treatment at 5 mg/day, the dose of DONEPEZIL can be increased to 10 mg/day (once-a-day dosing). The maximum recommended daily dose is 10 mg. Doses greater than 10 mg/day have not been studied in clinical trials.

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 accepted guidelines (e.g. DSM IV, ICD 10). Therapy with donepezil should only be started if a caregiver is available who will regularly monitor drug intake for the patient. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of donepezil should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to donepezil cannot be predicted.

Upon discontinuation of treatment, a gradual abatement of the beneficial effects of DONEPEZIL is seen.

Renal and Hepatic Impairment:
A similar dose schedule can be followed for patients with renal impairment, as clearance of donepezil hydrochloride is not affected by this condition.

Due to possible increased exposure in mild to moderate hepatic impairment (see section 5.2), dose escalation should be performed according to individual tolerability. There are no data for patients with severe hepatic impairment.

Children and adolescents:
DONEPEZIL is not recommended for use in children and adolescents below 18 years of age.

4.3 CONTRAINDICATIONS
DONEPEZIL is contraindicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.
4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The use of DONEPEZIL in patients with severe Alzheimer’s dementia, other types of dementia or other types of memory impairment (e.g., age-related cognitive decline), has not been investigated.

Anaesthesia: DONEPEZIL, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Cardiovascular Conditions: Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block.

There have been reports of syncope and seizures. In investigating such patients the possibility of heart block or long sinusual pauses should be considered.

Gastrointestinal Conditions: Patients at increased risk for developing ulcers, e.g. those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms. However, the clinical studies with DONEPEZIL showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Genitourinary: Although not observed in clinical trials of cholinomimetics may cause bladder outflow obstruction.

Neurological Conditions: Seizures: Cholinomimetics are believed to have some potential to cause generalised convulsions. However, seizure activity may also be a manifestation of Alzheimer’s Disease.

Cholinomimetics may have the potential to exacerbate or induce extrapyramidal symptoms.

Pulmonary Conditions: Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

The administration of DONEPEZIL concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided.

Severe Hepatic Impairment: There are no data for patients with severe hepatic impairment.

Mortality in Vascular Dementia Clinical Trials

Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients whose dementia appears to be due solely to vascular causes and to exclude patients with Alzheimer’s disease. In the first study, the mortality rates were 2/198 (1.0%) on donepezil hydrochloride 5 mg, 5/206 (2.4%) on donepezil hydrochloride 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on donepezil hydrochloride 5 mg and 0/326 (0%) on placebo. The mortality rate for the three VaD studies combined in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%), however, this difference was not statistically significant. The majority of deaths in patients taking either donepezil hydrochloride or placebo appear to result from various vascular related causes, which could be expected in this elderly population with underlying vascular disease. An analysis of all serious non-fatal and fatal vascular events showed no difference in the rate of occurrence in the donepezil hydrochloride group relative to placebo.

In pooled Alzheimer’s disease studies (n=4146), and when these Alzheimer’s disease studies were pooled with other dementia studies including the vascular dementia studies (total n=6888), the mortality rate in the placebo groups numerically exceeded that in the donepezil hydrochloride groups.
4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. The metabolism of donepezil hydrochloride is not affected by concurrent administration of digoxin or cimetidine. *In vitro* studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. Drug interaction studies performed *in vitro* show that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil metabolism. Therefore, these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine, could inhibit the metabolism of donepezil. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30%. Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care. Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity. There is also the potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists or beta blocking agents that have effects on cardiac conduction.

4.6 PREGNANCY AND LACTATION

Pregnancy:
There are no adequate data from the use of donepezil in pregnant women. Studies in animals have not shown teratogenic effect but have shown peri and post natal toxicity (see section 5.3 preclinical safety data). The potential risk for humans is unknown. DONEPEZIL should not be used during pregnancy unless clearly necessary.

Lactation:
Donepezil is excreted in the milk of rat. It is not known whether donepezil hydrochloride is excreted in human breast milk and there are no studies in lactating women. Therefore, women on donepezil should not breast feed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Donepezil has minor or moderate influence on the ability to drive and use machines.

Dementia may cause impairment of driving performance or compromise the ability to use machinery. Furthermore, donepezil can induce fatigue, dizziness and muscle cramps, mainly when initiating or increasing the dose. The treating physician should routinely evaluate the ability of patients on donepezil to continue driving or operating complex machines.

4.8 UNDESIRABLE EFFECTS

The most common adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10) common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10000) and not known (cannot be estimated from available data).
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
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<td>Agitation**</td>
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<td></td>
<td>behaviour**</td>
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<td>Dizziness</td>
<td>Seizure*</td>
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<td></td>
<td></td>
<td>Insomnia</td>
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<td>Cardiac disorders</td>
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<td>Bradycardia</td>
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<td>Sino-atrial block</td>
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<td>Atroventricular</td>
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<td>hepatitis***</td>
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<td>Skin and subcutaneous tissue</td>
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<td>Pruritus</td>
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<td>disorders</td>
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<td>Musculoskeletal, connective tissue</td>
<td>Muscle cramps</td>
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<tr>
<td>and bone disorders</td>
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<td>Renal and urinary disorders</td>
<td>Urinary incontinence</td>
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<td>Headache</td>
<td>Fatigue</td>
<td>Minor increase in</td>
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<td>site conditions</td>
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<td>Pain</td>
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<td>of muscle creatine</td>
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<tr>
<td>Injury and poisoning</td>
<td>Accident</td>
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</tbody>
</table>

*In investigating patients for syncope or seizure the possibility of heart block or long sinusal pauses should be considered (see section 4.4)

**Reports of hallucinations, agitation and aggressive behaviour have resolved on dose-reduction or discontinuation of treatment.

***In cases of unexplained liver dysfunction, withdrawal of DONEPEZIL should be considered.

### 4.9 OVERDOSE

The estimated median lethal dose of donepezil hydrochloride following administration of a single oral dose in mice and rats is 45 and 32 mg/kg, respectively, or approximately 225 and 160 times the maximum recommended human dose of 10 mg per day. Dose-related signs of cholinergic stimulation were observed in animals and included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, fasciculation and lower body surface temperature.

Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

As in any case of overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for DONEPEZIL overdosage. Intravenous atropine
sulphate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether donepezil hydrochloride and/or its metabolites can be removed by dialysis (haemodialysis, peritoneal dialysis, or haemofiltration).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

The pharmacotherapeutic group: anti-dementia drugs; anticholinesterases; ATC-code N06DA02.

Donepezil hydrochloride is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is in vitro over 1000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme that is present mainly outside the central nervous system.

Alzheimer’s Dementia

In patients with Alzheimer’s Dementia participating in clinical trials, administration of single daily doses of 5 mg or 10 mg of DONEPEZIL produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively when measured post dose. The inhibition of acetylcholinesterase (AChE) in red blood cells by donepezil hydrochloride has been shown to correlate to changes in ADAS-cog, a sensitive scale that examines selected aspects of cognition. The potential for donepezil hydrochloride to alter the course of the underlying neuropathology has not been studied. Thus, DONEPEZIL can not be considered to have any effect on the progress of the disease.

Efficacy of treatment of Alzheimer’s Dementia with DONEPEZIL has been investigated in four placebo-controlled trials, 2 trials of 6-month duration and 2 trials of 1-year duration.

In the 6 months clinical trial, an analysis was done at the conclusion of donepezil treatment using a combination of three efficacy criteria: the ADAS-Cog (a measure of cognitive performance), the Clinician Interview Based Impression of Change with Caregiver Input (a measure of global function) and the Activities of Daily Living Subscale of the Clinical Dementia Rating Scale (a measure of capabilities in community affairs, home and hobbies and personal care).

Patients who fulfilled the criteria listed below were considered treatment responders.

Response = Improvement of ADAS-Cog of at least 4 points
No deterioration of CIBIC +
No Deterioration of Activities of Daily Living Subscale of the Clinical Dementia Rating Scale

<table>
<thead>
<tr>
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<th>% Response</th>
<th>Intent to Treat Population</th>
<th>Evaluable Population</th>
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<tr>
<td>Placebo Group</td>
<td>10%</td>
<td>n = 365</td>
<td>10%</td>
</tr>
<tr>
<td>Donepezil tablets 5-mg Group</td>
<td>18%*</td>
<td></td>
<td>18%*</td>
</tr>
<tr>
<td>Donepezil tablets 10-mg Group</td>
<td>21%*</td>
<td></td>
<td>22%**</td>
</tr>
</tbody>
</table>

*p < 0.05
**p < 0.01

DONEPEZIL produced a dose-dependent statistically significant increase in the percentage of patients who were judged treatment responders.

5.2 PHARMACOKINETIC PROPERTIES

Absorption: Maximum plasma levels are reached approximately 3 to 4 hours after oral administration. Plasma concentrations and area under the curve rise in proportion to the dose. The terminal disposition half-life is approximately 70 hours, thus, administration of multiple single-daily doses results in gradual approach to steady-state. Approximate steady-state is achieved within 3 weeks after initiation of therapy. Once at steady-state, plasma donepezil hydrochloride
concentrations and the related pharmacodynamic activity show little variability over the course of the day.
Food did not affect the absorption of donepezil hydrochloride.

**Distribution:** Donepezil hydrochloride is approximately 95% bound to human plasma proteins. The plasma protein binding of the active metabolite 6-O-desmethyldonepezil is not known. The distribution of donepezil hydrochloride in various body tissues has not been definitively studied. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5 mg dose of $^{14}$C-labelled donepezil hydrochloride, approximately 28% of the label remained unrecovered. This suggests that donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

**Metabolism/Excretion:** Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of $^{14}$C-labelled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil hydrochloride (30%), 6-O-desmethyldonepezil (11% – only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyldonepezil (7%) and the glucuronide conjugate of 5-O-desmethyldonepezil (3%). Approximately 57% of the total administered radioactivity was recovered from the urine (17% as unchanged donepezil), and 14.5% was recovered from the faeces, suggesting biotransformation and urinary excretion as the primary routes of elimination. There is no evidence to suggest enterohepatic recirculation of donepezil hydrochloride and/or any of its metabolites.

Plasma donepezil concentrations decline with a half-life of approximately 70 hours.

Sex, race and smoking history have no clinically significant influence on plasma concentrations of donepezil hydrochloride. The pharmacokinetics of donepezil has not been formally studied in healthy elderly subjects, or in Alzheimer’s or vascular dementia patients. However, mean plasma levels in patients closely agreed with those of young healthy volunteers.

Patients with mild to moderate hepatic impairment had increased donepezil steady state concentrations; mean AUC by 48% and mean $C_{\text{max}}$ by 39% (see section 4.2).

5.3 PRECLINICAL SAFETY DATA
Extensive testing in experimental animals has demonstrated that this compound causes few effects other than the intended pharmacological effects consistent with its action as a cholinergic stimulator (see section 4.9). Donepezil is not mutagenic in bacterial and mammalian cell mutation assays. Some clastogenic effects were observed in vitro at concentrations overtly toxic to the cells and more than 3000 times the steady-state plasma concentrations. No clastogenic or other genotoxic effects were observed in the mouse micronucleus model in vivo. There was no evidence of oncogenic potential in long-term carcinogenicity studies in either rats or mice.

Donepezil hydrochloride had no effect on fertility in rats, and was not teratogenic in rats or rabbits, but had a slight effect on still-births and early pup survival when administered to pregnant rats at 50 times the human dose (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Mannitol
Colloidal anhydrous silica
κ-Carrageenan
Polyvinyl alcohol

6.2 INCOMPATIBILITIES
Not applicable.

6.3 SHELF LIFE
3 years
6.4 SPECIAL PRECAUTIONS FOR STORAGE
This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER
Blister (PVC/PVdC/PE/PVdC/PVC/Aluminium foil)
Pack sizes: 7, 14, 28, 30, 50, 56, 60, 98 or 120 tablets
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Eisai Ltd., European Knowledge Centre, Mosquito Way, Hatfield, Herts, AL10 9SN, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)
PL 10555/0036

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
20/04/2011

10 DATE OF REVISION OF THE TEXT
20/04/2011
1 NAME OF THE MEDICINAL PRODUCT
DONEPEZIL 10 mg orodispersible tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each orodispersible tablet contains 10 mg donepezil hydrochloride, equivalent to 9.12 mg of donepezil free base.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Orodispersible tablet.
Yellow orodispersible tablet embossed with “10” on one side.

4 CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
DONEPEZIL orodispersible tablets are indicated for the symptomatic treatment of:
- mild to moderately severe Alzheimer’s dementia

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
Adults/Elderly:
Treatment is initiated at 5 mg/day (once-a-day dosing). DONEPEZIL should be taken orally, in the evening, just prior to retiring. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference. The 5 mg/day dose should be maintained for at least one month in order to allow the earliest clinical responses to treatment to be assessed and to allow steady-state concentrations of donepezil hydrochloride to be achieved.
Following a one-month clinical assessment of treatment at 5 mg/day, the dose of DONEPEZIL can be increased to 10 mg/day (once-a-day dosing). The maximum recommended daily dose is 10 mg. Doses greater than 10 mg/day have not been studied in clinical trials.

Renal and Hepatic Impairment:
A similar dose schedule can be followed for patients with renal impairment, as clearance of donepezil hydrochloride is not affected by this condition.

Due to possible increased exposure in mild to moderate hepatic impairment (see section 5.2), dose escalation should be performed according to individual tolerability. There are no data for patients with severe hepatic impairment.

Children and adolescents:
DONEPEZIL is not recommended for use in children and adolescents below 18 years of age.

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DONEPEZIL is contraindicated in patients with a known hypersensitivity to donepezil hydrochloride, piperidine derivatives, or to any excipients used in the formulation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
The use of DONEPEZIL in patients with severe Alzheimer’s dementia, other types of dementia or other types of memory impairment (e.g., age-related cognitive decline), has not been investigated.

Anaesthesia: DONEPEZIL, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.
Cardiovascular Conditions: Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block.

There have been reports of syncope and seizures. In investigating such patients the possibility of heart block or long sinusal pauses should be considered.

Gastrointestinal Conditions: Patients at increased risk for developing ulcers, e.g. those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms. However, the clinical studies with DONEPEZIL showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Genitourinary: Although not observed in clinical trials of cholinomimetics may cause bladder outflow obstruction.

Neurological Conditions: Seizures: Cholinomimetics are believed to have some potential to cause generalised convulsions. However, seizure activity may also be a manifestation of Alzheimer's Disease.

Cholinomimetics may have the potential to exacerbate or induce extrapyramidal symptoms.

Pulmonary Conditions: Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

The administration of DONEPEZIL concomitantly with other inhibitors of acetylcholinesterase, agonists or antagonists of the cholinergic system should be avoided.

Severe Hepatic Impairment: There are no data for patients with severe hepatic impairment.

Mortality in Vascular Dementia Clinical Trials
Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients whose dementia appears to be due solely to vascular causes and to exclude patients with Alzheimer’s disease. In the first study, the mortality rates were 2/198 (1.0%) on donepezil hydrochloride 5 mg, 5/206 (2.4%) on donepezil hydrochloride 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on donepezil hydrochloride 5 mg and 0/326 (0%) on placebo. The mortality rate for the three VaD studies combined in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%), however, this difference was not statistically significant. The majority of deaths in patients taking either donepezil hydrochloride or placebo appear to result from various vascular related causes, which could be expected in this elderly population with underlying vascular disease. An analysis of all serious non-fatal and fatal vascular events showed no difference in the rate of occurrence in the donepezil hydrochloride group relative to placebo.

In pooled Alzheimer’s disease studies (n=4146), and when these Alzheimer’s disease studies were pooled with other dementia studies including the vascular dementia studies (total n=6888), the mortality rate in the placebo groups numerically exceeded that in the donepezil hydrochloride groups.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. The metabolism of donepezil hydrochloride is not affected by concurrent administration of digoxin or cimetidine. In vitro studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. Drug interaction studies performed in vitro show that ketoconazole and quinidine,
inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil metabolism. Therefore, these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine, could inhibit the metabolism of donepezil. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30%. Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care. Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity. There is also the potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists or beta blocking agents that have effects on cardiac conduction.

4.6 PREGNANCY AND LACTATION

Pregnancy:
There are no adequate data from the use of donepezil in pregnant women. Studies in animals have not shown teratogenic effect but have shown peri and post natal toxicity (see section 5.3 preclinical safety data). The potential risk for humans is unknown. DONEPEZIL should not be used during pregnancy unless clearly necessary.

Lactation:
Donepezil is excreted in the milk of rat. It is not known whether donepezil hydrochloride is excreted in human breast milk and there are no studies in lactating women. Therefore, women on donepezil should not breast feed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Donepezil has minor or moderate influence on the ability to drive and use machines.

Dementia may cause impairment of driving performance or compromise the ability to use machinery. Furthermore, donepezil can induce fatigue, dizziness and muscle cramps, mainly when initiating or increasing the dose. The treating physician should routinely evaluate the ability of patients on donepezil to continue driving or operating complex machines.

4.8 UNDESIRABLE EFFECTS

The most common adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10) common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10000) and not known (cannot be estimated from available data).
### System Organ Class

<table>
<thead>
<tr>
<th></th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td>Common cold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td>Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>Hallucinations** Agitation** Aggressive behaviour**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Syncope* Dizziness Insomnia</td>
<td>Seizure*</td>
<td>Extrapyramidal symptoms</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Bradycardia</td>
<td></td>
<td>Sino-atrial block Atrioventricular block</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea Nausea</td>
<td>Vomiting Abdominal disturbance</td>
<td>Gastrointestinal haemorrhage Gastric and duodenal ulcers</td>
<td>Liver dysfunction including hepatitis***</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Rash Pruritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td></td>
<td>Muscle cramps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Urinary incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Headache</td>
<td>Fatigue</td>
<td>Pain</td>
<td>Minor increase in serum concentration of muscle creatine kinase</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury and poisoning</td>
<td></td>
<td>Accident</td>
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</tr>
</tbody>
</table>

*In investigating patients for syncope or seizure the possibility of heart block or long sinusal pauses should be considered (see section 4.4)*

**Reports of hallucinations, agitation and aggressive behaviour have resolved on dose-reduction or discontinuation of treatment.***

***In cases of unexplained liver dysfunction, withdrawal of DONEPEZIL should be considered.

### 4.9 OVERDOSE

The estimated median lethal dose of donepezil hydrochloride following administration of a single oral dose in mice and rats is 45 and 32 mg/kg, respectively, or approximately 225 and 160 times the maximum recommended human dose of 10 mg per day. Dose-related signs of cholinergic stimulation were observed in animals and included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, fasciculation and lower body surface temperature.

Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved.

As in any case of overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for DONEPEZIL overdose. Intravenous atropine
sulphate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether donepezil hydrochloride and/or its metabolites can be removed by dialysis (haemodialysis, peritoneal dialysis, or haemofiltration).

5  PHARMACOLOGICAL PROPERTIES
5.1  PHARMACODYNAMIC PROPERTIES

The pharmacotherapeutic group: anti-dementia drugs; anticholinesterases; ATC-code N06DA02.

Donepezil hydrochloride is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is in vitro over 1000 times more potent an inhibitor of this enzyme than of butyrylcholinesterase, an enzyme that is present mainly outside the central nervous system.

Alzheimer’s Dementia
In patients with Alzheimer’s Dementia participating in clinical trials, administration of single daily doses of 5 mg or 10 mg of DONEPEZIL produced steady-state inhibition of acetylcholinesterase activity (measured in erythrocyte membranes) of 63.6% and 77.3%, respectively when measured post dose. The inhibition of acetylcholinesterase (AChE) in red blood cells by donepezil hydrochloride has been shown to correlate to changes in ADAS-cog, a sensitive scale that examines selected aspects of cognition. The potential for donepezil hydrochloride to alter the course of the underlying neuropathology has not been studied. Thus, DONEPEZIL can not be considered to have any effect on the progress of the disease.

Efficacy of treatment of Alzheimer’s Dementia with DONEPEZIL has been investigated in four placebo-controlled trials, 2 trials of 6-month duration and 2 trials of 1-year duration.

In the 6 months clinical trial, an analysis was done at the conclusion of donepezil treatment using a combination of three efficacy criteria: the ADAS-Cog (a measure of cognitive performance), the Clinician Interview Based Impression of Change with Caregiver Input (a measure of global function) and the Activities of Daily Living Subscale of the Clinical Dementia Rating Scale (a measure of capabilities in community affairs, home and hobbies and personal care).

Patients who fulfilled the criteria listed below were considered treatment responders.

Response = Improvement of ADAS-Cog of at least 4 points
No deterioration of CIBIC +
No Deterioration of Activities of Daily Living Subscale of the Clinical Dementia Rating Scale

<table>
<thead>
<tr>
<th></th>
<th>% Response</th>
<th>Intent to Treat Population n = 365</th>
<th>Evaluable Population n = 352</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Group</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Donepezil tablets 5-mg</td>
<td>18%*</td>
<td>18%*</td>
<td>18%*</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil tablets 10-mg</td>
<td>21%*</td>
<td></td>
<td>22%**</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05
**p < 0.01

DONEPEZIL produced a dose-dependent statistically significant increase in the percentage of patients who were judged treatment responders.

5.2  PHARMACOKINETIC PROPERTIES

Absorption: Maximum plasma levels are reached approximately 3 to 4 hours after oral administration. Plasma concentrations and area under the curve rise in proportion to the dose. The terminal disposition half-life is approximately 70 hours, thus, administration of multiple single-daily doses results in gradual approach to steady-state. Approximate steady-state is achieved within 3 weeks after initiation of therapy. Once at steady-state, plasma donepezil hydrochloride
concentrations and the related pharmacodynamic activity show little variability over the course of the day.
Food did not affect the absorption of donepezil hydrochloride.

Distribution: Donepezil hydrochloride is approximately 95% bound to human plasma proteins. The plasma protein binding of the active metabolite 6-O-desmethyldonepezil is not known. The distribution of donepezil hydrochloride in various body tissues has not been definitively studied. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5 mg dose of $^{14}$C-labelled donepezil hydrochloride, approximately 28% of the label remained unrecovered. This suggests that donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

Metabolism/Excretion: Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of $^{14}$C-labelled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil hydrochloride (30%), 6-O-desmethyldonepezil (11% – only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyldonepezil (7%) and the glucuronide conjugate of 5-O-desmethyldonepezil (3%). Approximately 57% of the total administered radioactivity was recovered from the urine (17% as unchanged donepezil), and 14.5% was recovered from the faeces, suggesting biotransformation and urinary excretion as the primary routes of elimination. There is no evidence to suggest enterohepatic recirculation of donepezil hydrochloride and/or any of its metabolites.

Plasma donepezil concentrations decline with a half-life of approximately 70 hours.

Sex, race and smoking history have no clinically significant influence on plasma concentrations of donepezil hydrochloride. The pharmacokinetics of donepezil has not been formally studied in healthy elderly subjects, or in Alzheimer’s or vascular dementia patients. However, mean plasma levels in patients closely agreed with those of young healthy volunteers.

Patients with mild to moderate hepatic impairment had increased donepezil steady state concentrations; mean AUC by 48% and mean $C_{\text{max}}$ by 39% (see section 4.2).

5.3 PRECLINICAL SAFETY DATA
Extensive testing in experimental animals has demonstrated that this compound causes few effects other than the intended pharmacological effects consistent with its action as a cholinergic stimulator (see section 4.9). Donepezil is not mutagenic in bacterial and mammalian cell mutation assays. Some clastogenic effects were observed in vitro at concentrations overtly toxic to the cells and more than 3000 times the steady-state plasma concentrations. No clastogenic or other genotoxic effects were observed in the mouse micronucleus model in vivo. There was no evidence of oncogenic potential in long-term carcinogenicity studies in either rats or mice.

Donepezil hydrochloride had no effect on fertility in rats, and was not teratogenic in rats or rabbits, but had a slight effect on still-births and early pup survival when administered to pregnant rats at 50 times the human dose (see section 4.6).

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Mannitol
Colloidal anhydrous silica
κ-Carrageenan
Polyvinyl alcohol
Yellow Iron oxide (E172) (10 mg only)

6.2 INCOMPATIBILITIES
Not applicable.
6.3 **SHELF LIFE**  
3 years

6.4 **SPECIAL PRECAUTIONS FOR STORAGE**  
This medicinal product does not require any special storage conditions.

6.5 **NATURE AND CONTENTS OF CONTAINER**  
Blister (PVC/PVdC/PE/PVdC/PVC/Aluminium foil)  
Pack sizes: 7, 14, 28, 30, 50, 56, 60, 98 or 120 tablets

Not all pack sizes may be marketed.

6.6 **SPECIAL PRECAUTIONS FOR DISPOSAL**  
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**  
Eisai Ltd., European Knowledge Centre, Mosquito Way, Hatfield, Herts, AL10 9SN, United Kingdom.

8 **MARKETING AUTHORISATION NUMBER(S)**  
PL 10555/0037

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
20/04/2011

10 **DATE OF REVISION OF THE TEXT**  
20/04/2011
Module 3
Product Information Leaflets

PACKAGE LEAFLET: INFORMATION FOR THE USER
DONEPEZIL 5 mg Orodispersible Tablets
DONEPEZIL 10 mg Orodispersible Tablets
(Donepezil Hydrochloride)

You and your caregiver should read all of this leaflet carefully before you start taking this medicine.

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

IN THIS LEAFLET:
1. What DONEPEZIL is and what it is used for
2. Before you take DONEPEZIL
3. How to take DONEPEZIL
4. Possible side effects
5. How to store DONEPEZIL
6. Further information

1. WHAT DONEPEZIL IS AND WHAT IT IS USED FOR

DONEPEZIL (donepezil hydrochloride) belongs to a group of medicines called acetylcholinesterase inhibitors. DONEPEZIL increases the levels of a substance (acetylcholine) in the brain involved in memory function by slowing down the breakdown of acetylcholine.

It is used to treat the symptoms of dementia in people diagnosed as having mild and moderately severe Alzheimer’s disease. The symptoms include increasing memory loss, confusion and behavioural changes. As a result, sufferers of Alzheimer’s disease find it more and more difficult to carry out their normal daily activities.

DONEPEZIL is for use in adult patients only.

- muscle relaxants e.g. diazepam, succinylcholine
- general anaesthetic
- medicines obtained without a prescription e.g. herbal remedies

If you are going to have an operation that requires you to have a general anaesthetic, you should tell your doctor and the anaesthetist that you are taking DONEPEZIL. This is because your medicine may affect the amount of anaesthetic needed.

DONEPEZIL can be used in patients with kidney disease or mild to moderate liver disease. Tell your doctor first if you have kidney or liver disease. Patients with severe liver disease should not take DONEPEZIL.

Tell your doctor or pharmacist the name of your caregiver. Your caregiver will help you to take your medicine as it is prescribed.

Taking DONEPEZIL with food and drink
Food will not influence the effect of DONEPEZIL.
DONEPEZIL should not be taken with alcohol because alcohol may change its effect.

Pregnancy and breast-feeding
DONEPEZIL should not be used while breastfeeding.
If you are pregnant, or think you might be pregnant, ask your doctor for advice before taking any medicine.

Driving and using machines
Alzheimer’s disease may impair your ability to drive or operate machinery and you must not perform these activities unless your doctor tells you that it is safe to do so.
Also, your medicine can cause tiredness, dizziness and muscle cramp. If you experience any of these effects you must not drive or operate machinery.
2. BEFORE YOU TAKE DONEPEZIL

Do NOT take DONEPEZIL
- if you are allergic (hypersensitive) to donepezil hydrochloride, or to piperidine derivatives, or any of the other ingredients of DONEPEZIL listed in section 6.

Take special care with DONEPEZIL
Tell your doctor or pharmacist before starting to take DONEPEZIL if you have or have had:
- stomach or duodenal ulcers
- seizures (fits) or convulsions
- a heart condition (irregular or very slow heart beat)
- asthma or other long term lung disease
- liver problems or hepatitis
- difficulty passing urine or mild kidney disease

Also tell your doctor if you are pregnant or think you might be pregnant.

Taking other medicines
Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicine. This includes medicines that your doctor has not prescribed for you but which you have bought yourself from a chemist/pharmacist. It also applies to medicines you may take sometime in the future if you continue to take DONEPEZIL. This is because these medicines may weaken or strengthen the effects of DONEPEZIL.

Especially tell your doctor if you are taking any of the following types of medicines
- other Alzheimer's disease medicines, e.g. galantamine
- pain killers or treatment for arthritis e.g. aspirin, non-steroidal anti-inflammatory (NSAID) drugs such as ibuprofen, or diclofenac sodium
- anticholinergics medicines, e.g. tolterodine
- antibiotics e.g. erythromycin, rifampicin
- anti-fungal medicine e.g. ketoconazole
- anti-depressants e.g. fluoxetine
- anticonvulsants e.g. phenytoin, carbamazepine
- medication for a heart condition e.g. quinidine, beta-blockers (propanolol and atenolol)

3. HOW TO TAKE DONEPEZIL

How much DONEPEZIL should you take?
Usually, you will start by taking 5 mg (one white tablet) every night before you go to bed. After one month, your doctor may tell you to take 10 mg (one yellow tablet) every night before you go to bed.

The tablet should be placed on your tongue and allowed to disintegrate before swallowing, with or without water, according to your preference.

The tablet strength you will take may change depending on the length of time you have been taking the medicine and on what your doctor recommends. The maximum recommended dose is 10 mg each night.

Always follow your doctor's, or pharmacist's advice about how and when to take your medicine.

Do not alter the dose yourself without your doctor's advice.

For how long should you take DONEPEZIL?
Your doctor or pharmacist will advise you on how long you should continue to take your tablets. You will need to see your doctor from time to time to review your treatment and assess your symptoms.

If you stop taking DONEPEZIL
Do not stop taking the tablets unless told to do so by your doctor. If you stop taking DONEPEZIL, the benefits of your treatment will gradually fade away.

If you take more DONEPEZIL than you should
DO NOT take more than one tablet each day. Call your doctor immediately if you take more than you should. If you cannot contact your doctor, contact the local hospital Accident and Emergency department at once.

Always take the tablets and the carton with you to the hospital so that the doctor knows what has been taken.

Symptoms of overdosing include feeling and being sick, drooling, sweating, slow heart rate, low blood pressure (light-headedness or dizziness when standing), breathing
problems, losing consciousness and seizures (fits) or convulsions.

If you forget to take DONEPEZIL

If you forget to take a tablet, just take one tablet the following day at the usual time. Do not take a double dose to make up for a forgotten tablet.
If you forget to take your medicine for more than one week, call your doctor before taking any more medicine.

4. POSSIBLE SIDE EFFECTS

Like all medicines, DONEPEZIL can cause side effects, although not everybody gets them.
The following side effects have been reported by people taking DONEPEZIL.

Tell your doctor if you have any of these effects while you are taking DONEPEZIL.

Serious side effects:
You must tell your doctor immediately if you notice these serious side effects mentioned.
You may need urgent medical treatment.
• liver damage e.g. hepatitis. The symptoms of hepatitis are feeling or being sick, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine (affects 1 to 10 users in 10,000)
• stomach or duodenal ulcers. The symptoms of ulcers are stomach pain and discomfort (indigestion) felt between the navel and the breast bone (affects 1 to 10 users in 1,000).
• bleeding in the stomach or intestines. This may cause you to pass black tar like stools or visible blood from the rectum (affects 1 to 10 users in 1,000).
• seizures (fits) or convulsions (affects 1 to 10 users in 1,000)

Very common side effects (affects more than 1 user in 10):
• diarrhoea
• feeling or being sick
• headaches

6. FURTHER INFORMATION

What do DONEPEZIL orodispersible tablets contain?
• The active substance is donepezil hydrochloride. The 5 mg orodispersible tablet contains 5 mg of donepezil hydrochloride and the 10 mg orodispersible tablet contains 10 mg of donepezil hydrochloride.
• The other ingredients are mannitol, colloidal anhydrous silica, k-carrageenan, and polyvinyl alcohol.
• Additionally, the 10 mg orodispersible tablet contains synthetic yellow iron oxide (E172).

What do DONEPEZIL orodispersible tablets look like?
• 5 mg white orodispersible tablets marked ‘5’ on one side.
• 10 mg yellow orodispersible tablets marked ‘10’ on one side.

What is in a pack of DONEPEZIL?
The orodispersible tablets are supplied in packs of 7, 14, 28, 30, 50, 56, 60, 98 or 120. Not all pack sizes may be marketed.

The Marketing Authorisation Holder is:
Eisai Ltd.,
Mosquito Way
Hatfield
Hertfordshire
AL10 9SN
United Kingdom.

DONEPEZIL orodispersible tablets are manufactured for Eisai Ltd. by:
Pfizer PGM,
29, Route des Industries,
37530 Pocé-sur-Cisse,
France.
Common side effects (affects 1 to 10 users in 100):
- muscle cramp
- tiredness
- difficulty in sleeping (insomnia)
- the common cold
- loss of appetite
- hallucinations (seeing or hearing things that are not really there)
- agitation
- aggressive behaviour
- fainting
- dizziness
- stomach feeling uncomfortable
- rash
- itching
- passing urine uncontrollably
- pain
- accidents (patients may be more prone to falls and accidental injury)

Uncommon side effects (affects 1 to 10 users in 1,000):
- slow heart beat

Rare side effects (affects 1 to 10 users in 10,000):
- stiffness, shaking or uncontrollable movement especially of the face and tongue but also of the limbs

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

5. HOW TO STORE DONEPEZIL

DO NOT use DONEPEZIL after the expiry date that is printed on the label. The expiry date refers to the last day of that month.
This medicine does not require any special storage conditions. Keep out of the reach and sight of children.
If your doctor tells you to stop taking your medicine, you should return any you have not used to your pharmacist.
Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
Module 4
Labelling

Each orodispersible tablet contains 5 mg donepezil hydrochloride equivalent to 4.56 mg donepezil free base. Use as directed by your physician. Read the package leaflet before use. Oral administration only. Keep out of the reach and sight of children. This medicinal product does not require any special storage conditions. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to your preference.
Donepezil 5 mg orodispersible tablets
donepezil hydrochloride
98 orodispersible tablets

Each orodispersible tablet contains 5 mg donepezil hydrochloride equivalent to 4.56 mg donepezil free base. Use as directed by your physician. Read the package leaflet before use. Oral administration only. Keep out of the reach and sight of children. This medicinal product does not require any special storage conditions. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to your preference.
Donepezil 10 mg orodispersible tablets

donepezil hydrochloride

28 orodispersible tablets

MAH: Eisai Ltd., Mosquito Way, Hatfield, Herts., AL10 9SN, UK.
By agreement, marketed by Eisai Ltd. and Pfizer Ltd.

PL 10555/0037

Each orodispersible tablet contains 10 mg donepezil hydrochloride equivalent to 9.12 mg donepezil free base. Use as directed by your physician. Read the package leaflet before use. Oral administration only. Keep out of the reach and sight of children. This medicinal product does not require any special storage conditions. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to your preference.
Each orodispersible tablet contains 10 mg donepezil hydrochloride equivalent to 9.12 mg donepezil free base. Use as directed by your physician. Read the package leaflet before use. Oral administration only. Keep out of the reach and sight of children. This medicinal product does not require any special storage conditions. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to your preference.
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Austria (AT), Belgium (BE), Germany (DE), Denmark (DK), Greece (EL), France (FR), Ireland (IE), Italy (IT), Luxembourg (LU), Portugal (PT), Sweden (SE) and the UK considered that the applications for Donepezil 5 mg and 10 mg orodispersible tablets could be approved. Donepezil 5 mg and 10 mg orodispersible tablets are prescription only medicines (POM) and are indicated for the symptomatic treatment of mild to moderately severe Alzheimer’s dementia.

These applications for Donepezil 5 mg and 10 mg orodispersible tablets were submitted according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Aricept Evess 5 mg and 10 mg orodispersible tablets (PL 10555/0019-20), first authorised to Eisai Limited on 17th May 2005.

Donepezil hydrochloride, a piperidine derivative, is a centrally active, reversible inhibitor of acetylcholinesterase. A deficiency of acetylcholine caused by selective loss of cholinergic neurons in the cerebral cortex, nucleus basalis, and hippocampus is recognised as one of the early pathophysiologic features of Alzheimer’s disease associated with memory loss and cognitive deficits. Since the resultant cortical deficiency of this neurotransmitter is believed to account for some of the clinical manifestations of mild to moderate dementia, enhancement of cholinergic function with an anticholinesterase agent, such donepezil, is one of the pharmacologic approaches to treatment. Due to the fact that widespread degeneration of multiple central neuronal systems eventually occurs in patients with Alzheimer’s disease, the potentially beneficial effects of anticholinesterase agents would diminish as the disease process advances and fewer cholinergic neurons remain functioning.

No new data were submitted nor were they necessary for these “simple” applications, as the data are identical to that of the previously granted cross-reference products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for non-submission of a Risk Management Plan.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Donepezil 5 mg and 10 mg orodispersible tablets</th>
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<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Donepezil hydrochloride</td>
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<td>Pharmacotherapeutic classification (ATC code)</td>
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<td>Reference numbers for the Decentralised Procedure</td>
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<td>Marketing Authorisation Number(s)</td>
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<td>Name and address of the authorisation holder</td>
<td>Eisai Ltd.</td>
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<td>European Knowledge Centre</td>
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<td>Mosquito Way, Hatfield</td>
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III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Donepezil hydrochloride

Chemical names:
1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-yl)methyl] piperidine hydrochloride.

Structural formula:

![Structural formula image]

Molecular formula: \( \text{C}_{24}\text{H}_{29}\text{NO}_3\text{HCl} \)

Appearance: White to off-white crystalline powder
Solubility: Soluble in water and methylene chloride
Molecular weight: 416.0

The source of the active substance is in-line with the source of the active substance for the cross-reference products.

All aspects of the manufacture of the active substance from its starting materials, specification, container closure system and stability are identical to the cross-reference products.

P. Medicinal Product

Other Ingredients

The composition is consistent with the details registered for the cross-reference products. There is one minor difference in product appearance. The proposed tablets have either a ‘5’ or ‘10’ embossed on the tablet surface depending on the product strength. The reference tablets have markings of either ‘5’ or ‘10’ on one side and ‘Aricept’ on the other. This is not considered to have a negative impact on the product quality and no other changes are proposed.

None of the excipients used contain material of human origin. This is confirmed by a statement from the Quality Expert. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as those intended for human consumption. The supplier of magnesium stearate has confirmed that it is of vegetable origin. This information is consistent with the cross-reference products.

Pharmaceutical Development

The objective of the development programme was to produce safe, efficacious products containing donepezil hydrochloride that could be considered identical products of Aricept Evess 5 mg and 10 mg orodispersible tablets.

The product development sections are identical to the cross-reference products.
Manufacturing Process
The manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.

The manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size for each product is stated.

Finished Product Specification
The finished product specifications are in-line with the details registered for the cross-reference products.

Container-Closure System
These products are packaged in:
i) Blisters composed of polyvinyl chloride (PVC), polyvinylidene chloride (PVDC), polyethylene (PE) and aluminium. The products come in pack sizes of 7, 14, 28, 30, 50, 56, 60, 98 and 120 orodispersible tablets.

Stability of the product
The proposed shelf-life is 3 years with no special storage conditions.
This is consistent with the details registered for the cross-reference products.

Summary of Product Characteristics (SmPCs), Patient Information Leaflets (PILs), Labels
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK approved PIL and labels are included in modules 3 and 4 of this report.

The patient information leaflet has been prepared in-line with the details registered for the cross-reference product. User testing results have been submitted for the film-coated cross-reference products, Aricept 5 mg and 10 mg film coated tablets (PL 10555/0006-7), which is identical to Aricept Evess 5 mg and 10 mg orodispersible tablets (PL 10555/0019-20) with the exception of the name, ingredients in the formulation and minor difference in the instructions for how to take the tablet. As the proposed PIL is in line with the reference PIL the need for additional testing is not considered necessary.

The results of consultations with target patient groups ("user testing") are in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that they contain.

The artwork is comparable to the artwork registered for the cross-reference product and complies with statutory requirements.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.
Conclusion
It is recommended that Marketing Authorisations are granted for these applications.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of donepezil hydrochloride are well-known. As donepezil hydrochloride is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required.

The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

An Environmental Risk Assessment has not been submitted and one is not required as these are applications for products which are identical to currently approved cross-reference products and there is no reason to conclude that marketing of this product will change the overall use pattern of the existing market.

It is recommended that Marketing Authorisations are granted for these applications from a non-clinical point of view.
III.3 CLINICAL ASPECTS

CLINICAL PHARMACOLOGY
No new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

EFFICACY
No new efficacy data were submitted with these applications and none were required.

SAFETY
No new safety data were submitted with these applications and none were required.

No new pharmacokinetic, pharmacodynamic, efficacy or safety data were submitted with these applications and none were required as these are ‘simple’ applications, which are duplicates of the currently approved cross-reference products. As the products applied for are essentially identical to those already marketed by the same company and the product literature is essentially identical, this is satisfactory. The clinical overview on the clinical pharmacology, efficacy and safety is considered adequate.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPCS), PATIENT INFORMATION LEAFLETS (PILS) AND LABELLING
The SmPCs, PIL and labelling are medically satisfactory and consistent with those for the cross-reference products, where appropriate.

CLINICAL EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA FORM
The MAA Forms are medically satisfactory.

CONCLUSIONS
It is recommended that Marketing Authorisations are granted for these applications.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The data for these applications are consistent with those previously approved for the cross-reference products and, as such, has been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are identical to the previously granted applications, Aricept Evess 5 mg and 10 mg orodispersible tablets (PL 10555/0019-20), first authorised to Eisai Limited on 17th May 2005.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with that for the cross-reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with donepezil hydrochloride is considered to have demonstrated the therapeutic value of the compounds. The risk:benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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