Public Assessment Report

Decentralised Procedure

Donepezil 5mg and 10mg Film Coated Tablets
UK/H/1807/001-002/DC

UK licence no: PL 32619/0001-2

Labormed-Pharma SA
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Labormed-Pharma SA Marketing Authorisations (licences) for the medicinal products Donepezil Hydrochloride 5mg and 10mg Film Coated Tablets (PL 32619/0001-2) on 6th March 2009. This is a prescription-only medicine used to treat the symptoms of dementia (disorder of rational behaviour) in people diagnosed as having mild to moderately severe Alzheimer’s disease (a chronic mental disease).

The tablets contain the active ingredient, donepezil hydrochloride. Donepezil hydrochloride belongs to a group of medicine called acetylcholinesterase inhibitor. Donepezil is well characterised in the literature. It is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Donepezil hydrochloride 5mg and 10mg Film-Coated Tablets outweigh the risks; hence Marketing Authorisations have been granted.
# TABLE OF CONTENTS

| Module 1: Information about initial procedure | Page 4 |
| Module 2: Summary of Product Characteristics   | Page 5 |
| Module 3: Product Information Leaflet         | Page 19 |
| Module 4: Labelling                           | Page 21 |
| Module 5: Scientific Discussion               | Page 29 |
| 1 Introduction                                | Page 29 |
| 2 Quality aspects                             | Page 31 |
| 3 Pre-clinical aspects                        | Page 33 |
| 4 Clinical aspects                            | Page 33 |
| 5 Overall conclusions                         | Page 37 |
| Module 6 Steps taken after initial procedure  | Page 38 |
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Donepezil 5mg and 10mg Film-Coated Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<td><strong>Active Substance</strong></td>
<td>Donepezil hydrochloride</td>
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<tr>
<td><strong>Form</strong></td>
<td>Film-Coated Tablet</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>5mg and 10mg</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Labormed Pharma S.A</td>
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<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
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<td><strong>CMS</strong></td>
<td>Romania and Bulgaria</td>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/1807/001-002/DC</td>
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<td><strong>Timetable</strong></td>
<td>Day 210 - 11/01/2009</td>
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</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Donepezil Hydrochloride 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 5 mg of donepezil hydrochloride, equivalent to 4.56 mg of donepezil free base.
Excipient: 79.32 mg of lactose monohydrate/film-coated tablet

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

White, round film-coated tablets with a diameter of 7.5 mm approximately.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Donepezil Hydrochloride film-coated 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 Hydrochloride should be taken orally, in the evening, just prior to retiring. 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 Hydrochloride 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 Hydrochloride 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
There is no relevant indication for the use of Donepezil Hydrochloride in children.

4.3 Contraindications
Hypersensitivity to the active substance, piperidine derivatives or to any of the excipients.
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 hydrochloride, 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 donepezil, 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 hydrochloride 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.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 neuromuscular blocking agents or cholinergic agonists or beta blocking agents which 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 Hydrochloride should not be used during pregnancy unless clearly necessary.

Lactation
Donepezil is excreted in the milk of rats. 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
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
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<tbody>
<tr>
<td>Infections and infestations</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
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<tr>
<td>Psychiatric disorders</td>
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<tr>
<td>Nervous system disorders</td>
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</tbody>
</table>

- Common cold
- Anorexia
- Hallucinations**
- Agitation**
- Aggressive behaviour**
- Syncope*
- Seizure*
- Extrapyramidal symptoms
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
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<tbody>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td>Dizziness</td>
<td>Bradycardia</td>
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<td></td>
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<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Nausea</td>
<td>Vomiting</td>
<td>Gastrointestinal haemorrhage</td>
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<td></td>
<td></td>
<td></td>
<td>Abdominal disturbance</td>
<td>Gastric and duodenal ulcers</td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td></td>
<td></td>
<td>Liver dysfunction including hepatitis***</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>Pruritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Muscle cramps</td>
<td></td>
<td></td>
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<tr>
<td>Renal and urinary disorders</td>
<td>Urinary incontinence</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Headache</td>
<td>Fatigue</td>
<td></td>
<td>Minor increase in serum concentration of muscle creatine kinase</td>
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<tr>
<td>Investigations</td>
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<tr>
<td>Injury and poisoning</td>
<td>Accident</td>
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</table>

*In investigating patients for syncope or seizure the possibility of heart block or long sinusual 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 Hydrochloride 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 Hydrochloride 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 (hemodialysis, peritoneal dialysis, or hemofiltration).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-dementia drugs; anticholinesterase.

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 butrylcholinesterase, 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 hydrochloride 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 which examines selected aspects of cognition. The potential for donepezil hydrochloride to alter the course of the underlying neuropathology has not been studied. Thus donepezil hydrochloride cannot be considered to have any effect on the progress of the disease.

Efficacy of treatment with donepezil hydrochloride 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>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>
</tr>
<tr>
<td>Donepezil 5-mg Group</td>
<td>18%*</td>
<td>18%*</td>
</tr>
<tr>
<td>Donepezil 10-mg Group</td>
<td>21%*</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-desmethyl donepezil (11% - only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyl donepezil (7%) and the glucuronide conjugate of 5-O-desmethyl donepezil (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
Tablet core:
- Lactose Monohydrate
- Maize starch
- Hydroxypropylcellulose
- Cellulose, Microcrystalline
- Magnesium Stearate

Film-coating:
- Opadry White:
- Hypromellose (E464)
- Titanium dioxide (E171)
- Propylene Glycol
- Talc

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Tablets are provided in blister packs (PVC-PE-PVDC/Aluminium blisters)
Pack sizes:
- 14, 28, 42, 56, 84, 98, 112 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
LaborMed Pharma S.A.
319E, Splaiul Independentei, 6th sector,
032258 Bucharest
Romania

8 MARKETING AUTHORISATION NUMBER(S)
PL 32619/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/03/2009

10 DATE OF REVISION OF THE TEXT
06/03/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Donepezil Hydrochloride 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 10 mg of donepezil hydrochloride, equivalent to 9.12 mg of donepezil.
Excipient: 158.64 mg of lactose monohydrate/film-coated tablet
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.
White, round film-coated tablets with a diameter of 9.3 mm approximately bearing a breakline on one side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Donepezil Hydrochloride film-coated 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 Hydrochloride should be taken orally, in the evening, just prior to retiring. 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 Hydrochloride 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.

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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 hydrochloride, 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.

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**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.

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

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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 neuromuscular blocking agents or cholinergic agonists or beta blocking agents which 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 Hydrochloride should not be used during pregnancy unless clearly necessary.

Lactation
Donepezil is excreted in the milk of rats. 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
Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common (≥1/10)</th>
<th>Common (≥1/100 to &lt;1/10)</th>
<th>Uncommon (≥1/1,000 to &lt;1/100)</th>
<th>Rare (≥1/10,000 to &lt;1/1,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
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<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
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<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Very Common (≥1/10)</td>
<td>Common (≥1/100 to &lt;1/10)</td>
<td>Uncommon (≥1/1000 to &lt;1/100)</td>
<td>Rare (≥1/10000 to &lt;1/1000)</td>
</tr>
<tr>
<td>--------------------------------------------</td>
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<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Bradycardia</td>
<td>Gastrointestinal haemorrhage</td>
<td>Sino-atrial block</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Insomnia</td>
<td></td>
<td>Gastric and duodenal ulcers</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Vomiting</td>
<td>Gastrointestinal haemorrhage</td>
<td>Liver dysfunction including hepatitis***</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Abdominal disturbance</td>
<td>Gastric and duodenal ulcers</td>
<td></td>
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<tr>
<td>Hepato-biliary disorders</td>
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<td></td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
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<tr>
<td></td>
<td>Pruritis</td>
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<td></td>
<td></td>
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<tr>
<td>Musculoskeletal, connective tissue and bone disorders</td>
<td>Muscle cramps</td>
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<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></td>
<td>Minor increase in serum concentration of muscle creatine kinase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury and poisoning</td>
<td>Accident</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*In investigating patients for syncope or seizure the possibility of heart block or long sinus 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 Hydrochloride 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 Hydrochloride 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 (hemodialysis, peritoneal dialysis, or hemofiltration).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: anti-dementia drugs; anticholinesterase.

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 hydrochloride 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 which examines selected aspects of cognition. The potential for donepezil hydrochloride to alter the course of the underlying neuropathology has not been studied. Thus donepezil hydrochloride cannot be considered to have any effect on the progress of the disease.

Efficacy of treatment with donepezil hydrochloride 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
Donepezil 5mg and 10mg Film-Coated Tablets

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Donepezil 5-mg Group</td>
<td>18%*</td>
<td>18%*</td>
</tr>
<tr>
<td>Donepezil 10-mg Group</td>
<td>21%*</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 14C-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 14C-labelled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil hydrochloride (30%), 6-O-desmethyl donepezil (11% - only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyl donepezil (7%) and the glucuronide conjugate of 5-O-desmethyl donepezil (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 Cmax 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
Tablet core:
Lactose Monohydrate
Maize starch
Hydroxypropylcellulose
Cellulose, Microcrystalline
Magnesium Stearate

Film-coating:
Opadry White:
Hypromellose (E464)
Titanium dioxide (E171)
Propylene Glycol
Talc

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Tablets are provided in blister packs (PVC-PE-PVDC/Aluminium blisters)
Pack sizes:
14, 28, 42, 56, 84, 98, 112 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
LaborMed Pharma S.A.
319E, Splaiul Independentei, 6th sector,
032258 Bucharest
Romania

8 MARKETING AUTHORISATION NUMBER(S)
PL 32313/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
06/03/2009

10 DATE OF REVISION OF THE TEXT
06/03/2009
Module 3
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Donepezil Hydrochloride 5 mg film-coated tablets
Donepezil Hydrochloride 10 mg film-coated tablets
(Donepezil Hydrochloride)

Do not take Donepezil Hydrochloride:
- if you are allergic (hypersensitive) to donepezil hydrochloride, or to any of the other ingredients of the tablets
- if you have ever had a seizure
- if you have a heart condition
- if you have asthma (dyspnoea) or other long term lung disease
- if you have ever had any liver problems or hepatitis
- if you have difficulty passing urine
- if you have taken Donepezil Hydrochloride before

Taking Donepezil Hydrochloride with food and drink
Donepezil Hydrochloride should be taken with liquid (a glass of water). Food does not have any effect on this medication.

Alcohol consumption should be restricted when taking donepezil, as alcohol may reduce the levels of donepezil.

Pregnancy and breast-feeding
If you are pregnant, think you might be pregnant or are breast-feeding, do not use Donepezil Hydrochloride.

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
A lifetime’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 fatigue, dizziness and muscle cramps and if affected you must not drive or operate machinery.

Important information about some of the ingredients of Donepezil Hydrochloride
This medicine contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE DONEPEZIL HYDROCHLORIDE
Always take Donepezil Hydrochloride exactly as your doctor has told you. You should check with your doctor or your pharmacist if you are not sure. Take your Donepezil Hydrochloride tablet by mouth with a drink of water at night before you go to bed.

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 will recommend.

Usually, you will start by taking 5mg every night.

After one month, your doctor may tell you to take 10 mg every night. The maximum recommended dose is 10 mg each night.

If you take more Donepezil Hydrochloride than you should:
Do not take more than one tablet each day. If you accidentally take too many tablets, the following symptoms may appear: nausea, vomiting, excess production of saliva, sweating, slow heart beat, low blood pressure, difficulty in breathing, muscle weakening, faint and fits (body shakes uncontrollably).

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.

**If you forget to take Donepezil Hydrochloride**

If you forget to take your medicine, but remember to take it after a short time, take that day's dose as usual.

However, if a long delay has occurred (e.g. all day), skip that dose and take the next dose the next day at the usual time and skip the forgotten dose. Do not take a double dose to make up for a forgotten tablet.

**If you stop taking Donepezil Hydrochloride**

Do not stop taking the tablets unless told to do so by your doctor.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Donepezil Hydrochloride can have side effects, although not everybody gets them.

In most cases these go away without having to stop treatment. Tell your doctor if you have any of these side effects and they are too uncomfortable for you.

Patients taking Donepezil Hydrochloride have reported the following side effects:

Very common side effects *(estimated frequency is more than 1 person out of 10)*

- diarrhea
- nausea
- headache

Common side effects *(estimated frequency is less than 1 person out of 10 but more than 1 out of 100)*

- common cold
- abdominal discomfort
- loss of appetite
- rash
- hallucinations
- itching
- agitation
- muscle cramps
- aggressive behavior
- urinary incontinence
- fainting
- fatigues
- dizziness
- pain
- insomnia (difficulty in sleeping)
- accident
- vomiting

Uncommon side effects *(estimated frequency is less than 1 person out of 100 but more than 1 out of 1000)*

- seizures
- abdominal bleeding
- slow heartbeat
- stomach and duodenal ulcers
- minor increase in serum concentration of muscle creatine kinase

Rare side effects *(estimated frequency is less than 1 person out of 1000 but more than 1 out of 10000)*

- shaking
- liver disorders including hepatitis
- stiffness or uncontrollable movement especially of the sartorial block, face and tongue but also of cardiac and cerebrovascular block 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 your pharmacist.

5. HOW TO STORE DONEPEZIL HYDROCHLORIDE

Keep out of the reach and sight of children.

Do not store above 30°C.

Do not use Donepezil Hydrochloride tablets after the expiry date which is stated on the blisters and the carton after <EXP>. The expiry date refers to the last day of that month.

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.

6. FURTHER INFORMATION

**What Donepezil Hydrochloride contains**

The active substance in Donepezil Hydrochloride tablets is donepezil hydrochloride.

5 mg tablet: each tablet contains 5 mg of donepezil hydrochloride, equivalent to 4.56 mg of donepezil free base.

10 mg tablet: each tablet contains 10 mg of donepezil hydrochloride, equivalent to 9.12 mg of donepezil free base.

The other ingredients are:

**Tablet core:**

Lactose Monohydrate, Microcrystalline Hydroxypropylcellulose, Cellulose, Magnesium Stearate

**Film-coating:**

Eudragit E, Titanium dioxide (E171), Propylene Glycol, Talc

**What Donepezil Hydrochloride looks like and contents of the pack**

5 mg tablet: white, round film-coated tablets with a diameter of 7.5 mm approximately.

10 mg tablet: white, round film-coated tablets with a diameter of 9.3 mm approximately bearing a breakline on one side.

The tablet can be divided into equal halves.

**Pack sizes:**

14, 28, 42, 56, 84, 98, 112 tablets

Not all pack sizes may be marketed.

**Marketing Authorisation Holder:**

LaborMed Pharmaceuticals S.A.
319E, Splaiul Independentei, 6th Sector, 032258 Bucharest, Romania

**Manufacturer:**

Laboromed Pharmaceuticals S.A.
44B Theodor Pallady str., 3rd Sector 032258 Bucharest, Romania

**Specialities:**

1, 25 Octombrie str., Ar. Vârvara 12351 Athens, Greece

This medicinal product is authorised in the member states of the EEA under the following names:

Donepezil Hydrochloride 5 mg: 10 mg film-coated tablets (United Kingdom)

Prada 5 mg: 10 mg film-coated tablets (Romania)

Donepezil LPH 5 mg: 10 mg film-coated tablets (Bulgaria)

This leaflet was last approved in 01.2009
Module 4
Labelling

Carton-Donepezil 5mg Film Coated Tablets (14 tablets)

Carton-Donepezil 5mg Film Coated Tablets (28 tablets)
Carton-Donepezil 5mg Film Coated Tablets (42 tablets)

Carton-Donepezil 5mg Film Coated Tablets (56 tablets)
Carton-Donepezil 5mg Film Coated Tablets (84 tablets)

Carton-Donepezil 5mg Film Coated Tablets (98 tablets)
Carton-Donepezil 5mg Film Coated Tablets (112 tablets)

Blister foil- Donepezil 5mg Film Coated Tablets
Carton-Donepezil 10mg Film Coated Tablets (42 tablets)

Carton-Donepezil 10mg Film Coated Tablets (56 tablets)
Carton-Donepezil 10mg Film Coated Tablets (84 tablets)

Carton-Donepezil 10mg Film Coated Tablets (98 tablets)
Carton-Donepezil 10mg Film Coated Tablets (112 tablets)

Blister foil- Donepezil 10mg Film Coated Tablets
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the
application for Donepezil 5mg and 10mg Film Coated Tablets, in the treatment of mild to
moderately severe Alzheimer’s dementia is approvable.

This application is made under Article 10.1 of 2001/83 EC, as amended, Donepezil 5mg and
10mg Film Coated Tablets, have been shown to be generic products of Aricept 5mg and
10mg Film Coated Tablets (PL 10555/0006-7) which were first granted to Eisai Ltd, UK
since 1997, over 10 years ago.

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.

No new preclinical or clinical studies were conducted and none are required for an
application of this type. This application for a generic product refers to Aricept 5mg and
10mg Film Coated Tablets, which has been licensed within the EEA for over 10 years. The
RMS has been assured that acceptable standards of GMP are in place for these product types
at all sites responsible for the manufacture, batch release and assembly of this product.

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 of 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 has been reassured that the submitted studies have been carried out in accordance
with GCP, and agreed ethical principles.

A package leaflet has been submitted to the MHRA along with results of consultations with
target patient groups ("user testing"), 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 it contains.
### II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Donepezil 5mg and 10mg Film Coated Tablets |
| Name(s) of the active substance(s) (INN)          | Donepezil Hydrochloride                  |
| Pharmacotherapeutic classification (ATC code)    | N06DA02 anti-dementia drugs; Anticholinesterases |
| Pharmaceutical form and strength(s)             | Film-Coated Tablet, 5mg and 10mg          |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1807/01-02/DC        |
| Reference Member State                          | United Kingdom                           |
| Member States concerned                         | Bulgaria and Romania                     |
| Marketing Authorisation Number(s)               | PL 32619/0001-2                          |
| Name and address of the authorisation holder     | Labormed-Pharma SA                        |
|                                                   | Splau Independientei SA 319E             |
|                                                   | Sector 6, Bucharest                       |
|                                                   | Romania                                  |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

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

Structure:

![Structure of Donepezil](image)

Molecular formula
C_{24}H_{30}ClNO_{3}

Molecular weight
415.95 g/mol

General Properties
Characteristics: White to off-white or slightly yellow crystalline powder

Solubility
Donepezil Hydrochloride is freely soluble in chloroform, dichloromethane and in methanol, soluble in water, sparingly soluble in ethanol, n-butanol and in acetonitrile and very slightly soluble in acetone.

Polymorphism:
Donepezil has one chiral centre thus it exhibits optical isomerism.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

The drug substance donepezil hydrochloride is not the subject of BP or Ph.Eur monographs. An appropriate specification is provided for the active substance donepezil hydrochloride. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active donepezil hydrochloride is stored in appropriate packaging that comply with Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs. Specifications and certificates of analysis have been provided.

Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for standards used by the active substance manufacturer during validation studies.
Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. The data demonstrates the stability of the drug substance and supports an appropriate retest period when stored in the proposed packaging.

P. Medicinal Product
Other Ingredients
Other ingredients consist of pharmaceutical excipients namely microcrystalline cellulose, lactose monohydrate, maize starch, magnesium stearate and hydroxypropylcellulose. All ingredients within the tablet body comply with relevant Ph Eur monographs.

The tablet coating contains: hypromellose (E464), titanium dioxide (E171) and propylene glycol and talc. All the ingredients within the tablets coating comply with their relevant Ph Eur monographs. Appropriate justification for the inclusion of each excipient has been provided.

Satisfactory certificates of analysis have been provided for all excipients.

With the exception of lactose none of the excipients used contain material derived from animal or human origin. The applicant has provided a declaration that milk used in the production of lactose is sourced from healthy animals under the same conditions as that for human consumption.

Pharmaceutical development
The formulation objective was to develop generic film-coated tablets bioequivalent to the reference product, Aricept 5mg and 10mg Tablets.

The objectives of the development programme were to develop a formula and a manufacturing process for Donepezil Hydrochloride Film Coated Tablets, to produce tablets with the following

1) comparable dissolution profile to the brand
2) bioequivalent to the brand
3) meet all physical and chemical specifications for the dosage form in general and for this product.

Dissolution and impurity profiles
Dissolution and impurity profiles for all both strengths of drug product were found to be similar to those for the reference products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process.

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.
Container-Closure System
Donepezil hydrochloride tablets are packaged in blister packs composed of polyvinyl chloride (PVC)/polyethylene (PE)/polyvinylidene chloride (PVdC)/aluminium. Blister pack presentation is available in pack sizes of 14, 28, 42, 56, 84, 98 and 112 film-coated tablets. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies have been performed on the three pilot-scale batches of 5mg strength and three pilot-scale batches of 10mg strength. All batches are packaged in the proposed commercial packaging. Stability testing is performed according to the relevant ICH guidelines. Based on the results of the stability studies, the applicant has proposed a shelf life of 3 years, with storage conditions of “Do not store above 30°C”. These are acceptable.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), 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 it contains.

Conclusion
The grant of marketing authorisations is recommended.

III.2 PRE-CLINICAL ASPECTS
No new preclinical data were supplied with this application and none are required. Clinical experience with Donepezil HCL overrides the need for further preclinical data. The nonclinical overview provides a satisfactory review of the relevant preclinical pharmacological and toxicological literature and has been written by an adequately qualified person.

III.3 CLINICAL ASPECTS

Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview dated 30 November 2006 has been written by a Doctor of Medicine with relevant experience in the pharmaceutical industry. The report refers to 221 publications up to 2006.

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Clinical study reports
To support the application, the applicant has submitted a single bioequivalence study: an open label, single dose, randomised, 2 way study of crossover design, performed under fasting conditions. The study was performed at the 10mg dose strength.

Biowaiver
The multiple strengths exemption criterion for linear pharmacokinetics over the therapeutic range is met.
The company’s clinical expert has provided the following justification for studying the 10mg strength only, rather than both strengths:

a. The pharmacokinetics are linear
b. The qualitative composition is the same
c. The ratio between active substance and the excipients in both strengths of the test product is the same
d. The dissolution rate of the highest strength of the test product in-vitro is similar to that of the lower strength, and the dissolution rate of both of the strengths of the test product in vitro is similar to the dissolution rates of the corresponding strengths of the reference product.

Assessor's comment:
A review of the PK characteristics of donepezil indicates that absorption is predictable and it appears unlikely that the conclusion of bioequivalence would be any different if the 5mg dose had also been studied. It is normally considered that the highest dose strength is the most discriminatory for the purposes of bioequivalence testing, which is the strength which has been tested here. The confidence intervals for the bioequivalence parameters of the presented studies are within the required limits by a substantial margin.

In conclusion the use of the 10mg strength only for the bioequivalence studies has been adequately justified and the results of Study 60455 with the 10mg formulation can be extrapolated to other strength 5mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Pharmacokinetic Studies

Study 60455
Study design
A comparative, randomised, two-way, two-period, single dose crossover study performed in fasting subjects.

Healthy fasting volunteers, aged 24-55 years, were randomised to receive a single dose of 10mg orally of either the applicant's test product or the reference product donepezil.

The randomisation scheme was balanced for sequence and appears random.

Serum drug levels were followed for 288 hours following dosing and the schedule was appropriate for accurate determination of \( \text{AUC}_{\text{inf}} \) and \( \text{C}_{\text{max}} \). The washout period between phases was 28 days.

Assessor's comment
Satisfactory study protocol.

Test and reference products:
Reference: Aricept 10mg Film Coated Tablets (Donepezil Hydrochloride) (Pfizer laboratories, France).
Test: Donepezil 10mg Film Coated Tablets (Donepezil Hydrochloride) (Specifar S.A., Greece).

Assessor's comment:
The comparator product is the EEA product to which essential similarity is claimed and is therefore satisfactory.

Population(s) studied
26 healthy fasted state adult volunteers were randomised and 16 completed the study
Assessor's comment:
No concerns raised.

Analytical methods
Plasma samples were analysed to quantify the concentration of donepezil using a validated LC/MS/MS bioanalytical method. The validation report has been provided. The linearity range for donepezil was 100.16 pg/ml to 25040.00 pg/ml and the lower limit of quantification was 100.16 pg/ml.

Pharmacokinetic Variables
Assessor's comment:
Conventional bioequivalence criteria.

Statistical methods
ANOVA for AUC, C<sub>max</sub>. Non-parametric for T<sub>max</sub>. Analysis of sequence/period effects.

Assessor's comment:
Conventional statistical methods.

Results

Table 1. Pharmacokinetic parameters for parent drug (non-transformed values; arithmetic mean ± SD, t<sub>max</sub>, median, range).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (Donepezil HCl (A))</th>
<th>Reference (Aricept (B))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;tot&lt;/sub&gt; (pg h/mL)</td>
<td>669298.34</td>
<td>180502.00</td>
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<tr>
<td>AUC&lt;sub&gt;t-ad&lt;/sub&gt; (pg h/mL)</td>
<td>729673.34</td>
<td>205820.66</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>17068.63</td>
<td>2303.61</td>
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<tr>
<td>Residual area (%)</td>
<td>8.06</td>
<td>2.99</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2.90</td>
<td>1.45</td>
</tr>
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<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>2.00</td>
<td>2.50</td>
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<tr>
<td>K&lt;sub&gt;el&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.0079</td>
<td>0.0015</td>
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<tr>
<td>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>91.14</td>
<td>22.51</td>
</tr>
</tbody>
</table>

*Medians and interquartile ranges are presented.

Table 2. Pharmacokinetic parameters for parent drug (log-transformed values). N=16.
**Donepezil HCl (A) vs Aricept (B)**

<table>
<thead>
<tr>
<th></th>
<th>AUC_{0-\infty}</th>
<th>AUC_{0-t}</th>
<th>C_{max}</th>
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<tr>
<td>Ratio(^1)</td>
<td>99.81%</td>
<td>101.36%</td>
<td>104.63%</td>
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<tr>
<td>90% Geometric C.I.(^2)</td>
<td>94.93% to 104.92%</td>
<td>96.42% to 106.53%</td>
<td>95.98% to 114.05%</td>
</tr>
<tr>
<td>Intra-Subject CV</td>
<td>7.78%</td>
<td>7.78%</td>
<td>13.47%</td>
</tr>
</tbody>
</table>

\(^1\) Calculated using least-squares means according to the formula: \(\frac{(Donepezil\ HCl\ (A) - Aricept\ (B)) \times 100}{Donepezil\ HCl\ (A) + Aricept\ (B)}\)

\(^2\) 90% Geometric Confidence Interval using in-transformed data

**Assessor's comment:**

These results are within conventional bioequivalence criteria, with 90% confidence intervals between 80-125%. Note that for both subject 19 and subject 22, the baseline plasma donepezil concentrations at the beginning of period 2 were not zero, being 100.55 pg/ml and 102.72 pg/ml respectively. A planned washout period of 28 days, corresponding to 9 – 10 of the documented mean half lives of donepezil, should have been sufficient. In the presented study, there were longer than normal half lives detected (60-161 hours, with a mean of 83 and 91 hours for the reference and test products respectively). The baseline plasma donepezil concentrations were close to the lower limit of quantification and represented less than 5% of the C_{max}. These findings were not considered to reflect a deficiency in study design.

The data from these two subjects were included for the purposes of statistical analyses and this is satisfactory.

**Pharmacokinetic conclusion**

Based on the submitted bioequivalence study Donepezil 10mg film coated tablets are considered bioequivalent with Aricept 10mg Film Coated Tablets (Donepezil Hydrochloride) (Pfizer laboratories, France).

The results of study 60455 with the 10mg formulation can be extrapolated to the other strength, 5mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

**Post marketing experience**

Donecitil 5 and 10mg film coated tablets have a well-recognised efficacy and an acceptable level of safety in the indications approved for Donepezil, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

**Benefit-Risk Assessment**

The application contains an adequate review of published clinical data and the bioequivalence has been shown. Approval is recommended from the clinical point of view.
V OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The important quality characteristics of Donepezil 5mg and 10mg Film Coated Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

No new preclinical data were submitted and none are required for an application of this type.

Bioequivalence has been demonstrated between the applicant’s Donepezil 10mg Film Coated Tablets and Aricept 10mg Film Coated Tablets (Donepezil Hydrochloride) (Pfizer laboratories, France).

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the innovator products are interchangeable. Extensive clinical experience with donepezil hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
# Module 6

## STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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