

# **Public Assessment Report**

## **Decentralised Procedure**

### **Donepezil Hydrochloride 5mg and 10mg Film-coated tablets**

**UK/H/1196/01-02/DC**

**UK licence no: PL 31304/0001-2**

**Applicant: Symphar SP Z O O**

## LAY SUMMARY

The MHRA granted Symphar SP Z O O Marketing Authorisation (licence) for the medicinal product Donepezil hydrochloride 5mg and 10mg film-coated tablets (PL 31304/0001-2) on 2<sup>nd</sup> September 2008. This is a prescription-only medicine (POM) 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).

Donepezil hydrochloride belongs to a group of medicine called acetylcholinestrase inhibitor.

These are Decentralised applications for Donepezil hydrochloride 5mg and 10mg film-coated tablets submitted under Directive 2001/83/EC Article 10.1 cross referring to Aricept® 5 and 10mg film-coated tablets granted marketing authorisations in UK on February 1997. Hence the ten year rule is complied with.

No new or unexpected safety concerns arose from this application 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 24 |
| Module 5: Scientific Discussion                | Page 26 |
| 1 Introduction                                 |         |
| 2 Quality aspects                              |         |
| 3 Non-clinical aspects                         |         |
| 4 Clinical aspects                             |         |
| 5 Overall conclusions                          |         |
| Module 6   Steps taken after initial procedure | Page 37 |

## Module 1

|                            |   |
|----------------------------|---|
| <b>Product Name</b>        | Donepezil hydrochloride 5 mg and 10mg film-coated tablets |
| <b>Type of Application</b> | Generic, Article 10.1                                     |
| <b>Active Substance</b>    | Donepezil hydrochloride                                   |
| <b>Form</b>                | Film-Coated Tablets                                       |
| <b>Strength</b>            | 5mg and 10mg Film-Coated Tablets                          |
| <b>MA Holder</b>           | Symphar SP Z O O  |
| <b>RMS</b>                 | UK  |
| <b>CMS</b>                 | PL  |
| <b>Procedure Number</b>    | UK/H/1196/01-2/DC   |
| <b>Timetable</b>           | Day 210– 30 <sup>th</sup> April 2008                      |

## Module 2

### SUMMARY OF PRODUCT CHARACTERISTICS

#### 1 NAME OF THE MEDICINAL PRODUCT

Donepezil hydrochloride 5 mg film-coated tablets

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Donepezil hydrochloride 5 mg film-coated tablets:

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

Excipient: 79.32 mg of lactose monohydrate/ tablet

For full list of excipients, see section 6.1.

#### 3 PHARMACEUTICAL FORM

Film-coated tablet.

5 mg: White, round tablets with a diameter of 7.5 mm approximately.

#### 4 CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

Donepezil hydrochloride 5 mg 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 5 mg film-coated tablets 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 5 mg film-coated tablets 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 5 mg film-coated tablets 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 5 mg film-coated tablets in children.

#### 4.3 Contraindications

Donepezil hydrochloride 5 mg film-coated tablets 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 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 sinus 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 neuro-muscular 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 5 mg film-coated tablets 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:

| <b>System Organ Class</b>          | <b>Very Common<br/>(≥1/10)</b> | <b>Common<br/>(≥1/100 to &lt;1/10)</b>                    | <b>Uncommon<br/>(≥1/1,000 to &lt;1/100)</b> | <b>Rare<br/>(≥1/10,000 to &lt;1/1,000)</b> |
|------------------------------------|--------------------------------|---|---|--|
| Infections and infestations        |                                | Common cold   |   |  |
| Metabolism and nutrition disorders |                                | Anorexia  |   |  |
| Psychiatric disorders              |                                | Hallucinations**<br>Agitation**<br>Aggressive behaviour** |   |  |

|   |                     |                                   |   |   |
|---|---------------------|-----------------------------------|---|---|
| Nervous system disorders                              |                     | Syncope*<br>Dizziness<br>Insomnia | Seizure*  | Extrapyramidal symptoms                     |
| Cardiac disorders                                     |                     |                                   | Bradycardia   | Sino-atrial block<br>Atrioventricular block |
| Gastrointestinal disorders                            | Diarrhoea<br>Nausea | Vomiting<br>Abdominal disturbance | Gastrointestinal haemorrhage<br>Gastric and duodenal ulcers     |   |
| Hepato-biliary disorders                              |                     |                                   |   | Liver dysfunction including hepatitis***    |
| Skin and subcutaneous tissue disorders                |                     | Rash<br>Pruritis                  |   |   |
| Musculoskeletal, connective tissue and bone disorders |                     | Muscle cramps                     |   |   |
| Renal and urinary disorders                           |                     | Urinary incontinence              |   |   |
| General disorders and administration site conditions  | Headache            | Fatigue<br>Pain                   |   |   |
| Investigations  |                     |                                   | Minor increase in serum concentration of muscle creatine kinase |   |
| Injury and poisoning                                  |                     | Accident                          |   |   |

\*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 5 mg film-coated tablets 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 5 mg film-coated tablets 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

|                       | % Response                          |                               |
|-----------------------|-------------------------------------|-------------------------------|
|                       | Intent to Treat Population<br>n=365 | Evaluable Population<br>n=352 |
| Placebo Group         | 10%                                 | 10%                           |
| Donepezil 5-mg Group  | 18%*                                | 18%*                          |
| Donepezil 10-mg Group | 21%*                                | 22%**                         |

\* 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 <sup>14</sup>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 <sup>14</sup>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<sub>max</sub> 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

Hydroxypropyl cellulose  
Microcrystalline cellulose  
Magnesium Stearate

Film-coating:

Opadry White: HPMC 2910/Hypromellose 5 cP (E464), Titanium dioxide (E171), Propylene Glycol, Talc

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

30 months

**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: 28 tablets

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

SymPhar Sp. z o.o.  
ul. Włoska 1  
00-777 Warsaw  
Poland

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 31304/0001

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

02/09/2008

**10 DATE OF REVISION OF THE TEXT**

02/09/2008

**1 NAME OF THE MEDICINAL PRODUCT**

Donepezil hydrochloride 10 mg film-coated tablets

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Donepezil hydrochloride 10 mg film-coated tablets:

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

Excipient: 158.64 mg of lactose monohydrate/ tablet

For full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

Film-coated tablet.

10 mg: White, round tablets with a diameter of 9.3 mm approximately bearing a breakline on one side. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

**4 CLINICAL PARTICULARS****4.1 Therapeutic indications**

Donepezil hydrochloride 10 mg 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 10 mg film-coated tablets 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 10 mg film-coated tablets 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 10 mg film-coated tablets 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 10 mg film-coated tablets in children.

**4.3 Contraindications**

Donepezil hydrochloride 10 mg film-coated tablets 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 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 sinus 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 neuro-muscular 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 10 mg film-coated tablets 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:

| <b>System Organ Class</b>          | <b>Very Common<br/>(≥1/10)</b> | <b>Common<br/>(≥1/100 to &lt;1/10)</b>                    | <b>Uncommon<br/>(≥1/1,000 to &lt;1/100)</b> | <b>Rare<br/>(≥1/10,000 to &lt;1/1,000)</b> |
|------------------------------------|--------------------------------|---|---|--|
| Infections and infestations        |                                | Common cold   |   |  |
| Metabolism and nutrition disorders |                                | Anorexia  |   |  |
| Psychiatric disorders              |                                | Hallucinations**<br>Agitation**<br>Aggressive behaviour** |   |  |
| Nervous system disorders           |                                | Syncope*<br>Dizziness<br>Insomnia                         | Seizure*                                    | Extrapyramidal symptoms                    |

|   |                     |                                   |   |   |
|---|---------------------|-----------------------------------|---|---|
| Cardiac disorders                                     |                     |                                   | Bradycardia   | Sino-atrial block<br>Atrioventricular block |
| Gastrointestinal disorders                            | Diarrhoea<br>Nausea | Vomiting<br>Abdominal disturbance | Gastrointestinal haemorrhage<br>Gastric and duodenal ulcers     |   |
| Hepato-biliary disorders                              |                     |                                   |   | Liver dysfunction including hepatitis***    |
| Skin and subcutaneous tissue disorders                |                     | Rash<br>Pruritis                  |   |   |
| Musculoskeletal, connective tissue and bone disorders |                     | Muscle cramps                     |   |   |
| Renal and urinary disorders                           |                     | Urinary incontinence              |   |   |
| General disorders and administration site conditions  | Headache            | Fatigue<br>Pain                   |   |   |
| Investigations  |                     |                                   | Minor increase in serum concentration of muscle creatine kinase |   |
| Injury and poisoning                                  |                     | Accident                          |   |   |

\*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 10 mg film-coated tablets 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 10 mg film-coated tablets 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

|                       | % Response                          |                               |
|-----------------------|-------------------------------------|-------------------------------|
|                       | Intent to Treat Population<br>n=365 | Evaluable Population<br>n=352 |
| Placebo Group         | 10%                                 | 10%                           |
| Donepezil 5-mg Group  | 18%*                                | 18%*                          |
| Donepezil 10-mg Group | 21%*                                | 22%**                         |

\* 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 <sup>14</sup>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 <sup>14</sup>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<sub>max</sub> 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  
Hydroxypropyl cellulose  
Microcrystalline cellulose  
Magnesium Stearate

Film-coating:

Opadry White: HPMC 2910/Hypromellose 5 cP (E464), Titanium dioxide (E171), Propylene Glycol, Talc

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

30 months

**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: 28 tablets

**6.6 Special precautions for disposal**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

SymPhar Sp. z o.o.  
ul. Włoska 1  
00-777 Warsaw  
Poland

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 31304/0002

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

02/09/2008

**10 DATE OF REVISION OF THE TEXT**

02/09/2008

## Module 3

### PACKAGE LEAFLET: INFORMATION FOR THE USER Donepezil hydrochloride 5 mg film-coated tablets (Donepezil Hydrochloride)

Read all of this leaflet carefully before you start using 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 gets 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 hydrochloride 5 mg film-coated tablets is and what it is used for
- 2 Before you take Donepezil hydrochloride 5 mg film-coated tablets
- 3 How to take Donepezil hydrochloride 5 mg film-coated tablets
- 4 Possible side effects
- 5 How to store Donepezil hydrochloride 5 mg film-coated tablets
- 6 Further information

#### 1 WHAT DONEPEZIL HYDROCHLORIDE 5 MG FILM-COATED TABLETS IS AND WHAT IT IS USED FOR

Donepezil hydrochloride 5 mg film-coated tablets (donepezil hydrochloride) belongs to a group of medicines called acetylcholinesterase inhibitors. It is 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). It is for use only in adult patients.

#### 2 BEFORE YOU TAKE DONEPEZIL HYDROCHLORIDE 5 MG FILM-COATED TABLETS

**Do not take Donepezil hydrochloride 5 mg film-coated tablets**

You must not take Donepezil hydrochloride 5 mg film-coated tablets if:

- you are allergic to donepezil hydrochloride, or to piperidine derivatives, or to any of the ingredients used in the formulation
- you are pregnant, think you might be pregnant or are breast feeding

**Take special care with Donepezil hydrochloride 5 mg film-coated tablets**

Tell your doctor or pharmacist if:

- you have ever had stomach or duodenal ulcers
- you have ever had a seizure
- you have a heart condition
- you have asthma (dyspnoea) or other long term lung disease
- you have ever had any liver problems or hepatitis (inflammation of the liver)
- you have difficulty passing urine

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Always tell your doctor or pharmacist if you are using or receiving any of the following medicines in addition to Donepezil hydrochloride 5 mg film-coated tablets:

- pain killers or treatment for arthritis
- antibiotics or anti-fungal medicines (drugs destroying or inhibiting the growth of fungi)
- muscle relaxants
- anti-depressants (medicines against mental depressions)
- anticonvulsants (medicines used in prevention of the occurrence of several types of seizures)
  - medication for a heart condition.



2 1 3 1 3 2 1 3 9

If you are going to have an operation that requires you to have a general anaesthetic (narcosis) you should tell your doctor and the anaesthetist that you are taking Donepezil hydrochloride 5 mg film-coated tablets.

**Taking Donepezil hydrochloride 5 mg film-coated tablets with food and drink**

Donepezil hydrochloride 5 mg film-coated tablets 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 5 mg film-coated tablets. Ask your doctor or your pharmacist for advice before taking any medicine.

**Driving and using machines**

Do not drive because 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. Do not use any tool or machine because your medicine can cause fatigue, dizziness and muscle cramp and if affected you must not drive or operate machinery.

**Important information about some of the ingredients of Donepezil hydrochloride 5 mg film-coated tablets**

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

#### 3 HOW TO TAKE DONEPEZIL HYDROCHLORIDE 5 MG FILM-COATED TABLETS

Always take Donepezil hydrochloride 5 mg film-coated tablets 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 5 mg film-coated tablets 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 5 mg 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. You should 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. 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 take more Donepezil hydrochloride 5 mg film-coated tablets than you should**

Do not take more than one tablet each day. If you do, you may experience nausea, vomiting, salivation, sweating, bradycardia, hypotension, difficulty in breathing, collapse and convulsion. Call your doctor immediately or contact the local hospital. 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 5 mg film-coated tablets**

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

**If you stop taking Donepezil hydrochloride 5 mg film-coated tablets**

Do not stop taking the tablets unless told to do so by your doctor. If you have any further question on the use of this product, ask your doctor or your pharmacist.

**4 POSSIBLE SIDE EFFECTS**

Like all medicines, Donepezil hydrochloride 5 mg film-coated tablets 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 effects and if they are too uncomfortable for you.

Patients taking Donepezil hydrochloride 5 mg film-coated tablets have reported following side effects:

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

- diarrhoea
- nausea
- headaches

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

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>• common cold</li> <li>• loss of appetite</li> <li>• hallucinations</li> <li>• agitation</li> <li>• aggressive behaviour</li> <li>• fainting</li> <li>• dizziness</li> <li>• insomnia (difficulty in sleeping)</li> <li>• accidents</li> </ul> | <ul style="list-style-type: none"> <li>• vomiting</li> <li>• abdominal disturbances</li> <li>• rash</li> <li>• itching</li> <li>• muscle cramp</li> <li>• urinary incontinence</li> <li>• fatigue</li> <li>• pain</li> </ul> |
|---|--|

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

- seizures
- gastrointestinal haemorrhage
- slow heart beat
- stomach and duodenal ulcers
- minor increase in serum concentration of muscle creatine kinase

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

- liver disorders including hepatitis
- shaking
- sino-atrial block, atrioventricular block
- stiffness 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 your pharmacist.**

**5 HOW TO STORE DONEPEZIL HYDROCHLORIDE 5 MG FILM-COATED TABLETS**

Do not store above 30°C. Keep out of the reach and sight of children. Do not use Donepezil hydrochloride 5 mg film-coated tablets after the expiry date which is stated on the carton. 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 5 mg film-coated tablets contains**

The active substance in Donepezil hydrochloride 5 mg film-coated tablets is donepezil hydrochloride. Each tablet contains 5 mg of donepezil hydrochloride, equivalent to 4.56 mg of donepezil free base.

The other ingredients are:

**Tablet core:** Lactose Monohydrate, Maize starch, Hydroxypropyl cellulose, Microcrystalline cellulose, Magnesium Stearate

**Film-coating:** HPMC 2910/Hypromellose 5 cP (E464), Titanium dioxide (E171), Propylene Glycol, Talc

**What Donepezil hydrochloride 5 mg film-coated tablets looks like and contents of the pack**

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

**Packs:** 28 tablets.

**Marketing Authorisation Holder:**

SymPhar Sp. z o.o., ul. Włoska 1, 00-777 Warsaw, Poland

**Manufacturer:**

SymPhar Sp. z o.o., ul. Włoska 1, 00-777 Warsaw, Poland

Specifar S.A. 1, 28 Octovriou str.123 51 Ag. Varvara Athens, Greece

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

UK: Donepezil hydrochloride 5 mg film-coated tablets

PL: Sympezil

**This leaflet was last approved in 30.04.2008**



## PACKAGE LEAFLET: INFORMATION FOR THE USER

### Donepezil hydrochloride 10 mg film-coated tablets

(Donepezil Hydrochloride)

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
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- 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 gets 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 hydrochloride 10 mg film-coated tablets is and what it is used for
- 2 Before you take Donepezil hydrochloride 10 mg film-coated tablets
- 3 How to take Donepezil hydrochloride 10 mg film-coated tablets
- 4 Possible side effects
- 5 How to store Donepezil hydrochloride 10 mg film-coated tablets
- 6 Further information

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Donepezil hydrochloride 10 mg film-coated tablets (donepezil hydrochloride) belongs to a group of medicines called acetylcholinesterase inhibitors. It is 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). It is for use only in adult patients.

#### 2 BEFORE YOU TAKE DONEPEZIL HYDROCHLORIDE 10 MG FILM-COATED TABLETS

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You must not take Donepezil hydrochloride 10 mg film-coated tablets if:

- you are allergic to donepezil hydrochloride, or to piperidine derivatives, or to any of the ingredients used in the formulation
- you are pregnant, think you might be pregnant or are breast feeding

Take special care with Donepezil hydrochloride 10 mg film-coated tablets

Tell your doctor or pharmacist if:

- you have ever had stomach or duodenal ulcers
- you have ever had a seizure
- you have a heart condition
- you have asthma (dyspnoea) or other long term lung disease
- you have ever had any liver problems or hepatitis (inflammation of the liver)
- you have difficulty passing urine

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Always tell your doctor or pharmacist if you are using or receiving any of the following medicines in addition to Donepezil hydrochloride 10 mg film-coated tablets:

- pain killers or treatment for arthritis
- antibiotics or anti-fungal medicines (drugs destroying or inhibiting the growth of fungi)
- muscle relaxants
- anti-depressants (medicines against mental depressions)
- anticonvulsants (medicines used in prevention of the occurrence of several types of seizures)
  - medication for a heart condition.



If you are going to have an operation that requires you to have a general anaesthetic (narcosis) you should tell your doctor and the anaesthetist that you are taking Donepezil hydrochloride 10 mg film-coated tablets.

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Donepezil hydrochloride 10 mg film-coated tablets 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.

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If you are pregnant, think you might be pregnant or are breast feeding, do not use Donepezil hydrochloride 10 mg film-coated tablets. Ask your doctor or your pharmacist for advice before taking any medicine.

Driving and using machines

Do not drive because 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. Do not use any tool or machine because your medicine can cause fatigue, dizziness and muscle cramp and if affected you must not drive or operate machinery.

Important information about some of the ingredients of Donepezil hydrochloride 10 mg film-coated tablets

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

#### 3 HOW TO TAKE DONEPEZIL HYDROCHLORIDE 10 MG FILM-COATED TABLETS

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**If you stop taking Donepezil hydrochloride 10 mg film-coated tablets**

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

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

**4 POSSIBLE SIDE EFFECTS**

Like all medicines, Donepezil hydrochloride 10 mg film-coated tablets 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 effects and if they are too uncomfortable for you.

Patients taking Donepezil hydrochloride 10 mg film-coated tablets have reported following side effects:

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

- diarrhoea
- nausea
- headaches

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

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>• common cold</li> <li>• loss of appetite</li> <li>• hallucinations</li> <li>• agitation</li> <li>• aggressive behaviour</li> <li>• fainting</li> <li>• dizziness</li> <li>• insomnia (difficulty in sleeping)</li> <li>• accidents</li> </ul> | <ul style="list-style-type: none"> <li>• vomiting</li> <li>• abdominal disturbances</li> <li>• rash</li> <li>• itching</li> <li>• muscle cramp</li> <li>• urinary incontinence</li> <li>• fatigue</li> <li>• pain</li> </ul> |
|---|--|

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

- seizures
- gastrointestinal haemorrhage
- slow heart beat
- stomach and duodenal ulcers
- minor increase in serum concentration of muscle creatine kinase

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

- liver disorders including hepatitis
- shaking
- sino-atrial block, atrioventricular block
- stiffness 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 your pharmacist.**

**5 HOW TO STORE DONEPEZIL HYDROCHLORIDE 10 MG FILM-COATED TABLETS**

Do not store above 30°C. Keep out of the reach and sight of children. Do not use Donepezil hydrochloride 10 mg film-coated tablets after the expiry date which is stated on the carton. 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 10 mg film-coated tablets contains**

The active substance in Donepezil hydrochloride 10 mg film-coated tablets is donepezil hydrochloride. 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, Maize starch, Hydroxypropyl cellulose, Microcrystalline cellulose, Magnesium Stearate

Film-coating: HPMC 2910/Hypromellose 5 cP (E464), Titanium dioxide (E171), Propylene Glycol, Talc

**What Donepezil hydrochloride 10 mg film-coated tablets looks like and contents of the pack**

White, round film-coated tablets with a diameter of 9.3 mm approximately bearing a breakline on one side.

Packs: 28 tablets.

**Marketing Authorisation Holder:**

SymPhar Sp. z o.o., ul. Włoska 1, 00-777 Warsaw, Poland

**Manufacturer:**

SymPhar Sp. z o.o., ul. Włoska 1, 00-777 Warsaw, Poland

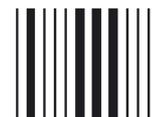
Specifar S.A. 1, 28 Octovriou str.123 51 Ag. Varvara Athens, Greece

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

UK: Donepezil hydrochloride 10 mg film-coated tablets

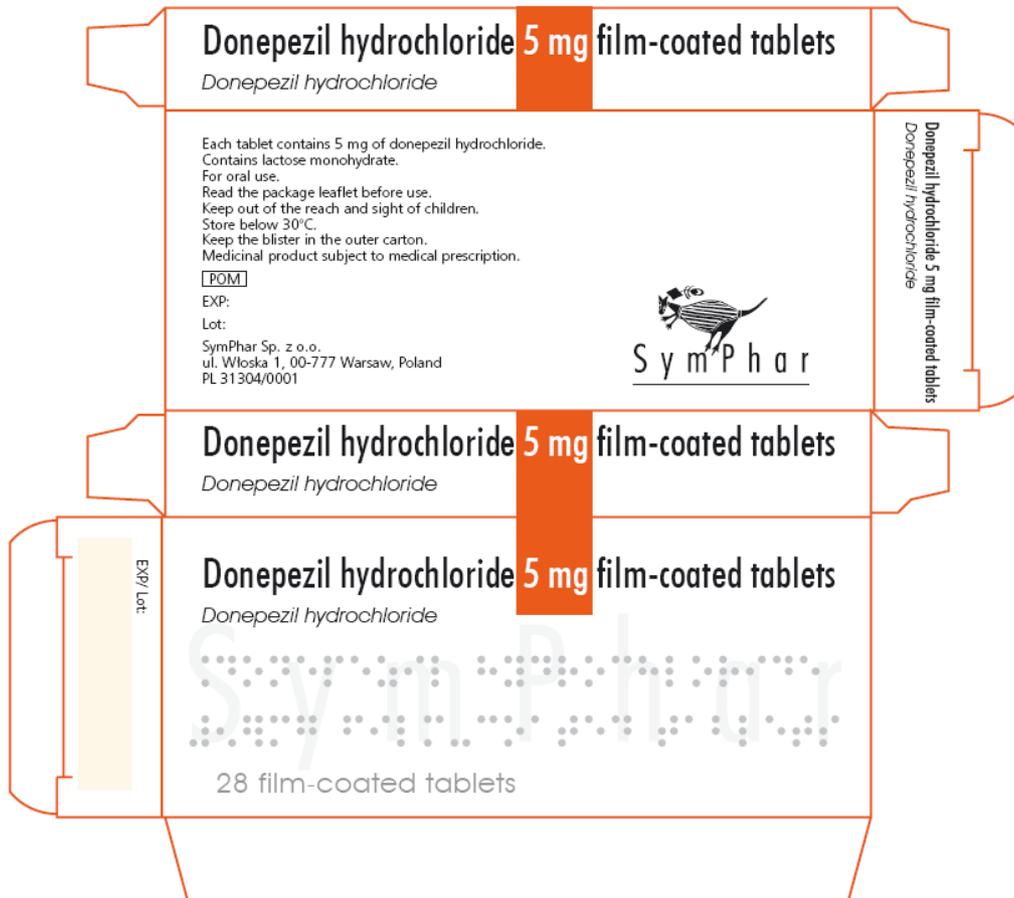
PL: Sympezil

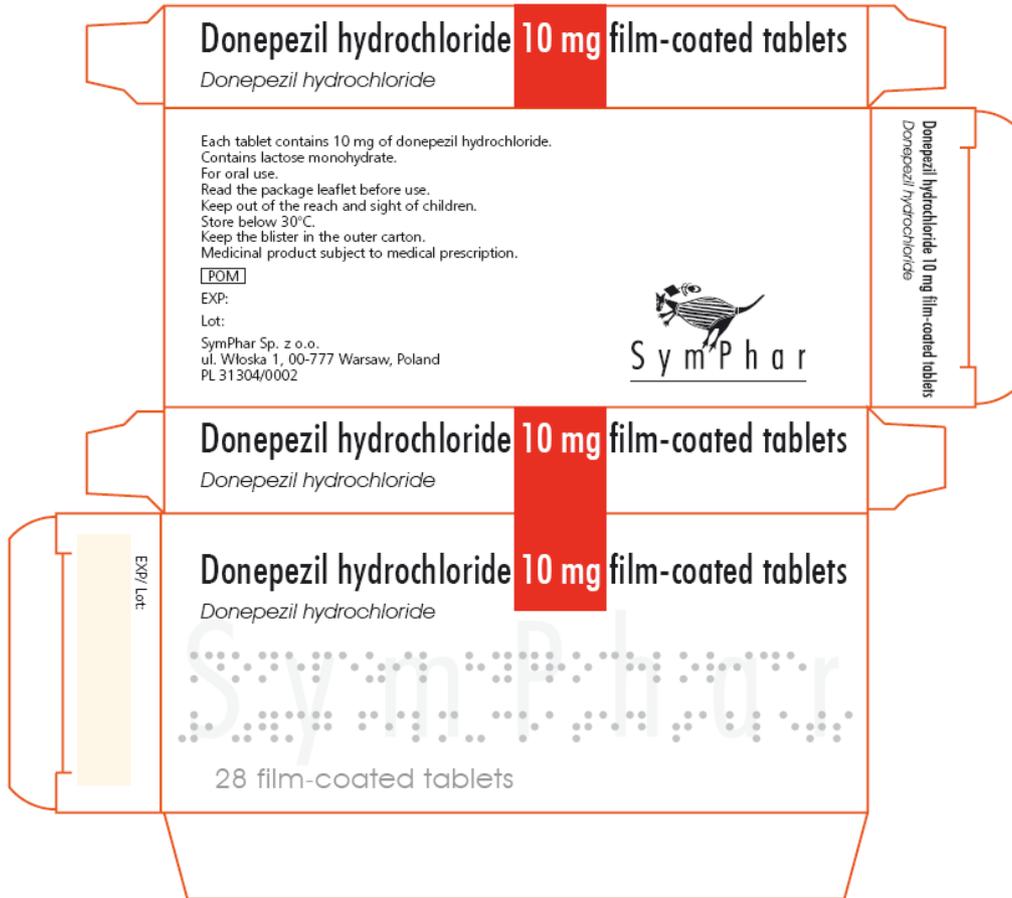
This leaflet was last approved in 30.04.2008



## Module 4

### LABELLING





## 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 applications for Donepezil hydrochloride 5mg and 10 mg film-coated tablets (PL 31304/0001-2) are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia could be approvable.

These are abridged applications for Donepezil hydrochloride 5mg-coated tablets and Donepezil hydrochloride 10mg film-coated tablets. These are two strengths of Donepezil, submitted under article 10.1 of Directive 2001/83/EC, as amended claiming to be generic medicinal products of the reference products Aricept Tablets 5mg and Aricept tablets 10mg (PL 10555/0006-7) respectively, granted to Eisai Limited on 14<sup>th</sup> February 1997. The reference products have been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Donepezil hydrochloride 5mg and 10mg Film-coated tablets contain the active ingredient donepezil, which is a drug for dementia. The products are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

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 butylcholinesterase, an enzyme that is present mainly outside the central nervous system.

Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3-4 hours. Pharmacokinetics are linear over the dose range 1-10mg. It circulates approximately 96% bound to human plasma proteins, mainly albumins. It is metabolised by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. The elimination half life is about 70 hours. It is both excreted in the urine intact and extensively metabolised to four major metabolites, two of which are known to be active, and a number of minor metabolites.

These applications for Donepezil hydrochloride 5mg and 10mg film-coated tablets were submitted at the same time and both depend on the bioequivalence study presented comparing the applicant's test 10mg strength product with the reference product Aricept 10mg Tablets, manufactured by Pfizer Laboratoire, France.

**II. ABOUT THE PRODUCT**

|  |  |
|--|--|
| Name of the product in the Reference Member State      | Donepezil Hydrochloride 5mg and 10mg Film-coated tablets |
| Name(s) of the active substance(s) (INN)               | Donepezil Hydrochloride                                  |
| Pharmacotherapeutic classification (ATC code)          | ATC Code: N06DA02  |
| Pharmaceutical form and strength(s)                    | Film-Coated Tablets 5mg and 10mg                         |
| Reference numbers for the Mutual Recognition Procedure | UK/H/1196/01-02/DC                                       |
| Reference Member State                                 | United Kingdom   |
| Member States Concerned                                | PL   |
| Marketing Authorisation Number(s)                      | PL 31304/0001-2  |
| Name and address of the authorisation holder           | Symphar SP ZOO, UL WLOSKA 1L<br>Warsaw PL 00-777 Poland  |

### III SCIENTIFIC OVERVIEW AND DISCUSSION

#### ACTIVE SUBSTANCE

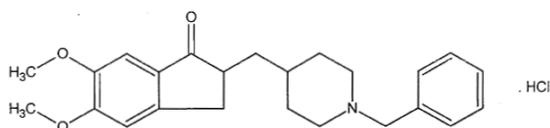
Donepezil hydrochloride

Nomenclature:

INN: Donepezil hydrochloride

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

Structure



Molecular Formula:  $C_{24}H_{29}NO_3 \cdot HCl$

Molecular Weight: 415.96

Physical form: White to off-white crystalline powder

Solubility: Soluble in chloroform sparingly soluble in water, methanol and acetic acid

The active substance, donepezil hydrochloride, is not the subject of a European Pharmacopoeia (EP) monograph.

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 specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Active donepezil hydrochloride is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated.

## **DRUG PRODUCT**

### **Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose, maize starch, magnesium stearate, Opadry 02H28525 White and water purified.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of OPADRY 02H28525 White which comply with in-House specifications.

Satisfactory certificates of analysis have been provided for all excipients.

The only excipients used that contain material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin.

### **Pharmaceutical development**

The proposed composition and manufacture is consistent with the details registered for the cross-reference product.

### **Dissolution and impurity profiles**

The dissolution and impurity profiles are consistent with the details registered for the cross-reference product.

### **Manufacture**

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

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

Satisfactory batch formulae have been provided for the manufacture of the product along with an appropriate account of the manufacturing process. The manufacturing process has been validated and appropriate in-process controls are applied.

### **Finished product specification**

The proposed finished product specification is in-line with the details registered for the cross-reference product.

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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**

Product is packaged in to PVC/PVDC, PE and aluminium Blister. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 30 months with storage conditions 'Do not store above 30 degrees C' has been set. This is satisfactory.

**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 proposed products are consistent with the details registered for the cross-reference products. It is recommended that Marketing Authorisations should be granted for these applications.

## **PRE-CLINICAL ASPECTS**

No new preclinical data have been supplied with this application and none are required for applications of this type.

## CLINICAL ASPECTS

### 1. INTRODUCTION

These are decentralised applications for film coated tablets containing 5 and 10mg of Donepezil as the hydrochloride. With the UK acting as the reference member state, the applicant also seeks marketing authorisations in Poland. These are abridged application, submitted under article 10.1 of directive 2001/83/EC, as amended.

The originator products are Aricept 5 and 10mg Film Coated Tablets (Eisai Ltd., UK), registered since 14/02/97. The UK reference products are Aricept 5 and 10mg Film Coated Tablets (Eisai Ltd., UK)

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 butylcholinesterase, an enzyme that is present mainly outside the central nervous system.

Donepezil film-coated tablets are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

### 2. INDICATIONS

Donepezil hydrochloride 5 mg and 10mg Film-coated Tablets are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

### 3. DOSE & DOSE SCHEDULE

#### *Adults/Elderly*

Treatment is initiated at 5 mg/day (once-a-day dosing). Donepezil hydrochloride 5 mg film-coated tablets 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 5 mg film-coated tablets 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 5 mg film-coated tablets 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 5 mg film-coated tablets in children.

#### **4. TOXICOLOGY**

No formal data are provided under this heading and none are required for this application.

#### **5. CLINICAL PHARMACOLOGY**

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:

The pharmacokinetics is linear. The qualitative composition is the same

The ratio between active substance and the excipients in both strengths of the test product is the same.

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 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 design

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

The randomisation scheme was balanced for sequence and appears random.

### *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.*

### *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.

### 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.

Table 2. Pharmacokinetic parameters for parent drug (log-transformed values). N=16.

| <b>Donepezil HCl (A) vs Aricept (B)</b> |                     |                      |                     |
|---|---------------------|----------------------|---------------------|
|   | AUC <sub>0-t</sub>  | AUC <sub>0-inf</sub> | C <sub>max</sub>    |
| Ratio <sup>1</sup>                      | 99.81%              | 101.36%              | 104.63%             |
| 90 % Geometric C.I. <sup>2</sup>        | 94.95 % to 104.92 % | 96.42 % to 106.55 %  | 95.98 % to 114.05 % |
| Intra-Subject CV                        | 7.78 %              | 7.78 %               | 13.47 %             |

<sup>1</sup> Calculated using least-squares means according to the formula:  $e^{(\text{Donepezil HCl (A)} - \text{Aricept (B)})} \times 100$

<sup>2</sup> 90% Geometric Confidence Interval using ln-transformed data

*Assessor's comment:*

## 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 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.

**6. EFFICACY**

No new data are submitted and none are required for these applications.

**7. SAFETY**

No new data are submitted and none are required for these applications.

**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.

## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|----------------|------------------|-------|---------|
|                |                  |       |         |
|                |                  |       |         |
|                |                  |       |         |
|                |                  |       |         |
|                |                  |       |         |