Public Assessment Report

Decentralised

Donepezil Hydrochloride 5mg and 10mg Film-coated Tablets

Donepezil hydrochloride

UK/H/1595/01-02/DC

Apotex Europe B.V.
Lay Summary

The Medicines and healthcare products regulatory Agency (MHRA) granted Apotex Europe BV Marketing Authorisations (licences) for the medicinal products Donepezil Hydrochloride 5mg and 10mg Film-coated Tablets (PL 27583/0063-4) on 03/08/2009. These are prescription only medicines.

Donepezil Hydrochloride 5mg and 10mg Film-coated Tablets contain the active ingredient donepezil hydrochloride and 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.

The data submitted in support of the application for Donepezil Hydrochloride 5mg and 10mg Film-coated Tablets raised no clinically significant safety concerns and it was therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation was granted.
## Module 1

<table>
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<th><strong>Product Name</strong></th>
<th>Donepezil Hydrochloride 5 mg and 10 mg film-coated tablets</th>
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<td><strong>Type of Application</strong></td>
<td>Complex Abridged Decentralised (Article 10.1)</td>
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<td><strong>Active Substance (INN)</strong></td>
<td>Donepezil Hydrochloride</td>
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<td><strong>Pharmacotherapeutic Classification (ATC)</strong></td>
<td>N06DA02: anti-dementia drugs; anticholinesterase</td>
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<td><strong>Pharmaceutical Form and Strength</strong></td>
<td>Film-coated Tablets, 5 and 10mg</td>
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<td><strong>Procedure Numbers</strong></td>
<td>UK/H/1595/01-02/DC</td>
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<td><strong>RMS</strong></td>
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<td><strong>CMS</strong></td>
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<td><strong>End Date</strong></td>
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<td><strong>MA Number</strong></td>
<td>PL 27583/0063-4</td>
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<tr>
<td><strong>Name and address of MA holder</strong></td>
<td>Apotex Europe B.V. Darwinweg 20 2333 CR Leiden The Netherlands</td>
</tr>
</tbody>
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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 5 mg film-coated tablet contains 5 mg donepezil hydrochloride equivalent to 4.56 mg donepezil free base.

Excipient: Lactose monohydrate. Each tablet contains 112.95 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Film-coated tablet.

White to off-white, round, biconvex, film-coated tablets, with ‘APO’ debossed on one side and ‘DO’ over ‘5’ on the other.

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 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 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 hydrochloride 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 hydrochloride 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 hydrochloride cannot be predicted.

Upon discontinuation of treatment, a gradual abatement of the beneficial effects of Donepezil hydrochloride 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:
Donepezil hydrochloride Film-coated tablets is not recommended for use in children.

4.3 Contraindications
Donepezil hydrochloride Film-coated tablets are 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 hydrochloride Film-coated tablets 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 Film-coated tablets, 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 hydrochloride Film-coated tablets 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 hydrochloride Film-coated tablets, 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 Film-coated tablets 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 NINDSAIREN 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 hydrochloride in pregnant women. Studies in animals have not shown teratogenic effect but have shown peri and post natal
toxicity (see section 5.3). The potential risk for humans is unknown. Donepezil hydrochloride Film-coated tablets should not be used during pregnancy unless clearly necessary.

**Lactation:**

Donepezil hydrochloride 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 hydrochloride should not breastfeed.

4.7 **Effects on ability to drive and use machines**

Donepezil hydrochloride 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 hydrochloride 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 hydrochloride to continue driving or operating complex machines.

4.8 **Undesirable effects**

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

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as:

- very common  $(\geq 1/10)$
- common  $(\geq 1/100, < 1/10)$,
- uncommon  $(\geq 1/1,000, < 1/100)$,
- rare  $(\geq 1/10,000, <1/1,000)$,
- very rare  $(< 1/10000)$ and
- not known  (cannot be estimated from available data).

**Infections and infestations:**

Common: common cold

**Metabolism and nutrition disorders:**

Common: anorexia

**Psychiatric disorders:**

Common: hallucinations**, agitation**, aggressive behaviour**
Nervous system disorders:
Common: syncope*, dizziness*, insomnia
Uncommon: seizure
Rare: extrapyramidal symptoms

Cardiac disorders:
Uncommon: bradycardia
Rare: sino-atrial block, atrioventricular block

Gastrointestinal disorders:
Very Common: diarrhoea, nausea
Common: vomiting, abdominal disturbance
Uncommon: gastrointestinal haemorrhage, gastric and duodenal ulcers

Hepato-biliary disorders:
Rare: Liver dysfunction including hepatitis***

Skin and subcutaneous tissue disorders:
Common: rash, pruritis

Musculoskeletal connective tissue and bone disorders:
Common: muscle cramps

Renal and urinary disorders:
Common: urinary incontinence

General disorders and administration site conditions:
Very common: headache
Common: fatigue, pain

Investigations:
Uncommon: minor increase in serum concentration of muscle creatine kinase

Injury and poisoning:
Common: accident

* 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 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, meiosis, fasciculation and lower body surface temperature.

Over dosage 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 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 Film-coated tablets 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 Film-coated tablets cannot be considered to have any effect on the progress of the disease.

Efficacy of treatment with Donepezil hydrochloride Film-coated tablets has been investigated in four placebocontrolled 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 hydrochloride treatment using a combination of three efficacy criteria: the ADAS-Cog (a measure of cognitive performance), the Clinician Interview Based Impression of Change with Caregiver Input (a measure of global function) and the Activities of Daily Living Subscale of the Clinical Dementia Rating Scale (a measure of capabilities in community affairs, home and hobbies and personal care).

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

Response = Improvement of ADAS-Cog of at least 4 points

No deterioration of CIBIC +

No Deterioration of Activities of Daily Living Subscale of the Clinical Dementia Rating Scale

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

* p<0.05
** p<0.01

Donepezil hydrochloride Film-coated tablets 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
- Microcrystalline cellulose
- Magnesium stearate

*Tablet coat:*
- Hypromellose (E464)
- Talc (E553b)
- Polyethylene glycol 8000
- Titanium dioxide (E171)

6.2 **Incompatibilities**
Not applicable.

6.3 **Shelf life**
2 years.
6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
PVC/Aluminium blister: 28, 30
White, round HDPE bottles with blue PP cap: 30, 100

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Apotex Europe BV
Darwinweg 20
2333 CR, Leiden
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)
PL 27583/0063

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
03/08/2009

10 DATE OF REVISION OF THE TEXT
03/08/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1  NAME OF THE MEDICINAL PRODUCT
   Donepezil hydrochloride 10 mg Film-coated tablets

2  QUALITATIVE AND QUANTITATIVE COMPOSITION
   Each 10 mg film-coated tablet contains 10 mg donepezil hydrochloride equivalent to 9.12 mg
   donepezil free base.

   Excipient: Lactose monohydrate. Each tablet contains 225.90 mg lactose monohydrate.

   For a full list of excipients, see section 6.1.

3  PHARMACEUTICAL FORM
   Film-coated tablet.

   Light yellow to yellow. round, biconvex, film-coated tablets, with ‘APO’ debossed on one
   side and ‘DO’ over ‘10’ on the other.

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 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 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 hydrochloride 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 hydrochloride 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 hydrochloride cannot be predicted.

Upon discontinuation of treatment, a gradual abatement of the beneficial effects of Donepezil hydrochloride 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:*
Donepezil hydrochloride Film-coated tablets is not recommended for use in children.

**4.3 Contraindications**
Donepezil hydrochloride Film-coated tablets are 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 hydrochloride Film-coated tablets 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 Film-coated tablets, 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 hydrochloride Film-coated tablets 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 hydrochloride Film-coated tablets, 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 Film-coated tablets 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 hydrochloride in pregnant women. Studies in animals have not shown teratogenic effect but have shown peri and post natal toxicity (see section 5.3). The potential risk for humans is unknown. Donepezil hydrochloride Film-coated tablets should not be used during pregnancy unless clearly necessary.

Lactation:
Donepezil hydrochloride 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 hydrochloride should not breast feed.

4.7 Effects on ability to drive and use machines
Donepezil hydrochloride 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 hydrochloride 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 hydrochloride to continue driving or operating complex machines.

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

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as:

- very common (≥ 1/10)
- common (≥ 1/100, <1/10)
- uncommon (≥ 1/1,000, <1/100)
- rare (≥ 1/10,000, <1/1,000)
- very rare (< 1/10000) and
- not known (cannot be estimated from available data).

Infections and infestations:
Common: common cold

Metabolism and nutrition disorders:
Common: anorexia

Psychiatric disorders:
Common: hallucinations**, agitation**, aggressive behaviour**

Nervous system disorders:
Common: syncope*, dizziness*, insomnia
Uncommon: seizure
Rare: extrapyramidal symptoms
Cardiac disorders:
Uncommon: bradycardia
Rare: sino-atrial block, atrioventricular block

Gastrointestinal disorders:
Very Common: diarrhoea, nausea
Common: vomiting, abdominal disturbance
Uncommon: gastrointestinal haemorrhage, gastric and duodenal ulcers

Hepato-biliary disorders:
Rare: Liver dysfunction including hepatitis***

Skin and subcutaneous tissue disorders:
Common: rash, pruritus

Musculoskeletal connective tissue and bone disorders:
Common: muscle cramps

Renal and urinary disorders:
Common: urinary incontinence

General disorders and administration site conditions:
Very common: headache
Common: fatigue, pain

Investigations:
Uncommon: minor increase in serum concentration of muscle creatine kinase

Injury and poisoning:
Common: accident

* 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 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, meiosis, fasciculation and lower body surface temperature.

Over dosage 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 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 Film-coated tablets 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 Film-coated tablets cannot be considered to have any effect on the progress of the disease.
Efficacy of treatment with Donepezil hydrochloride Film-coated tablets 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 hydrochloride 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>% 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 hydrochloride 5 mg Film-coated tablets Group</td>
<td>18 %*</td>
<td>18 %*</td>
</tr>
<tr>
<td>Donepezil hydrochloride 10 mg Film-coated tablets Group</td>
<td>21 %*</td>
<td>22 %**</td>
</tr>
</tbody>
</table>

* p<0.05
** p<0.01

Donepezil hydrochloride Film-coated tablets 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 singledaily 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
- Microcrystalline cellulose
- Magnesium stearate

*Tablet coat:*

- Hypromellose (E464)
- Talc (E553b)
- Polyethylene glycol 8000
- Titanium dioxide (E171)
- Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium blister: 28, 30
White, round HDPE bottles with blue PP cap: 30, 100

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
No special requirements.

7 **MARKETING AUTHORISATION HOLDER**
Apotex Europe BV
Darwinweg 20
2333 CR, Leiden
The Netherlands

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 27583/0064

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
03/08/2009

10 **DATE OF REVISION OF THE TEXT**
03/08/2009
Module 3

Product Information Leaflet
PACKAGE LEAFLET: INFORMATION FOR THE USER
Donepezil hydrochloride 5 mg Film-coated tablets
Donepezil hydrochloride 10 mg Film-coated tablets
(donepezil hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects 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 is and what it is used for
2. Before you take Donepezil
3. How to take Donepezil
4. Possible side effects
5. How to store Donepezil
6. Further information

1. WHAT DONEPEZIL IS AND WHAT IT IS USED FOR

Donepezil belongs to a group of medicines called ‘acetylcholinesterase inhibitors’.

Donepezil is used to treat the symptoms of dementia in people who have mild to moderately severe Alzheimer’s disease. Dementia is the gradual loss of mental abilities such as thinking, remembering and reasoning.

2. BEFORE YOU TAKE DONEPEZIL

Do not take Donepezil if:
- you are allergic (hypersensitive) to donepezil hydrochloride or any of the other ingredients in this medicine (listed in section 6).
- you are allergic (hypersensitive) to medicines that contain ‘piperidine derivatives’.

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking Donepezil.

Take special care with Donepezil
Check with your doctor or pharmacist before taking your medicine if:
- you have ever had an ulcer in your stomach or duodenum
- you have ever had a fit (seizure)
- you have any heart problems
- you have asthma or any other long term lung problems
- you have ever had any liver problems (hepatitis)
- you have difficulty in passing water (urine)
If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Donepezil.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines you get without a prescription.

Tell your doctor or pharmacist if you are taking any of the following:
- painkillers
- muscle relaxants such as succinylcholine
- antibiotics such as erythromycin or trimethoprim
- anti-fungal medicines such as ketoconazole or itraconazole
- medicines for arthritis
- medicines for depression such as fluoxetine
- medicines for high (sodium) such as phenytoin or carbamazepine
- medicines for heart problems such as beta blockers or quinidine.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking Donepezil.

3. HOW TO TAKE DONEPEZIL

Always take Donepezil exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking the medicine
- Take this medicine before you go to bed.
- Swallow the tablets whole with water.

How much to take

Adults
- The usual dose is one 5 mg tablet each night.
- After one month your doctor may increase the dose to one 10 mg tablet each night, if this is needed. This is the maximum recommended dose.

Children
Donepezil should not be given to children.
If you take more Donepezil than you should
If you take more Donepezil than you should, talk to a doctor or go to hospital straight away. Take the medicine pack with you.

If you forgot to take Donepezil
- If you forget a dose, skip the missed dose.
- Take the next dose as usual.
- Do not take a double dose to make up for a forgotten tablet.

If you stop taking Donepezil
Do not stop taking Donepezil without talking to your doctor.

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

4. POSSIBLE SIDE EFFECTS

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

The following side effects may happen with this medicine:

Very common (affects more than 1 in 10 people):
- diarrhoea or feeling sick (nausea)
- headache.

Common (affects less than 1 in 10 people):
- common cold
- seeing, hearing or feeling things that are not there (hallucinations)
- feeling agitated or aggressive
- being sick (vomiting), stomach pain, losing your appetite
- feeling tired or unable to sleep (insomnia), feeling dizzy, fainting
- a rash or itching
- muscle cramps
- loss of control of your bladder (incontinence).

Uncommon (affects less than 1 in 100 people):
- shaking
- slow heart beat
- ulcer in your stomach and duodenum.

Rare (affects less than 1 in 1,000 people):
- uncontrollable movements including fits (seizures)
- liver problems (hepatitis).

If any of the side effects gets serious, or if you notice any other side effects not listed in this leaflet, please tell your doctor or pharmacist. Your doctor may decide to reduce your dose or stop treatment.

5. HOW TO STORE DONEPEZIL

- Keep out of the reach and sight of children.
- This medicinal product does not require any special storage conditions.

Do not use Donepezil after the expiry date which is stated on the carton, blister and bottle 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 contains
- The active substance is donepezil hydrochloride.
- Each 5 mg tablet contains 5 mg donepezil hydrochloride corresponding to 4.56 mg donepezil.
- Each 10 mg tablet contains 10 mg donepezil hydrochloride corresponding to 9.12 mg donepezil.
- The other ingredients are lactose monohydrate, microcrystalline cellulose, magnesium stearate, hydroxypropyl cellulose (E464), talc (E552b), polyethylene glycol 6000 and titanium dioxide (E171). The 10 mg tablet also contains yellow iron oxide (E172).

What Donepezil looks like and contents of the pack
- The 5 mg tablets are white to off-white, round, biconvex, with 'APO' on one side and 'DC' over '5' on the other.
- The 10 mg tablets are light yellow to yellow, round, biconvex, with 'APO' on one side and 'DC' over '10' on the other.
- The tablets are available in blister packs of 28 and 30 tablets and bottles of 30 and 100 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Apotex Europe BV, Durvynweg 20, 2333 GR, Leiden, The Netherlands

Manufacturer: Apotex Nederland B.V., Archimedesweg 2, 2333 CN, Leiden, The Netherlands

This leaflet was last approved in June 2009.
Module 4

Labelling
Module 5

Scientific discussion during initial procedure

Based on the review of the data and the Applicant’s response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the application for Donepezil Hydrochloride in the treatment of mild to moderately severe Alzheimer's dementia, is approvable and a Marketing Authorisation was granted in the UK on 03/08/2009.

This report evaluates the chemical-pharmaceutical aspects of a decentralised application for Marketing Authorisation by Apotex Europe B.V., using the abridged procedure as described in Article 10(1) of Directive 2001/83/EC: Generic Application. Essential similarity with Aricept 5 and 10mg Film Coated Tablets (Eisai Ltd., UK) is claimed. The reference tablets were licensed in 1997 and have thus been authorised in the EU for more than 10 years. A bioequivalence study was performed using Aricept 10mg Film Coated Tablets (Eisai Ltd., UK) as the reference. The relevant products in the UK are Aricept 5 and 10mg Film Coated Tablets (Eisai Ltd., UK). The UK was RMS and the CMS were BE, PT, ES, LU, CZ, IT and PL.

About the product

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.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture 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.
SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance
The drug substance donepezil hydrochloride (rINN) is not the subject of European Pharmacopoeia monograph. Information on the drug substance is submitted in the form of drug master file.

The chemical-pharmaceutical documentation and Expert Report on the active drug substance from the named source in relation to Donepezil hydrochloride 5 and 10mg film-coated tablets is now adequately characterised and of sufficient quality in view of the present European regulatory requirements. The scale of synthesis and the method of manufacture employed are adequately detailed.

Donepezil has one chiral centre thus it exhibits optical isomerism. Donepezil hydrochloride produced by the DMF holders is a racemic mixture and exists in polymorphic Form I. To ensure the consistency of the racemic mixture, optical rotation limits are included in the drug substance specification.

The characterisation and control of drug substance may generally be considered satisfactory in view of the clarification now provided.

The HPLC method used for the determination of assay and related substances for donepezil hydrochloride (Form-I) has been adequately validated.

Stability studies have been performed with the drug substance at real time (25°C±2°C/60% ± 5% RH), intermediate storage (30°C±2°C and RH 65% ±5%) and under accelerated conditions (40°C±2°C/75% ± 5% RH) in line with ICH guidelines. At real time storage assay, related impurities and moisture/water content remains virtually unchanged. At real time storage (25°C±2°C/60% ± 5% RH) the polymorphic form (Form I) remains unchanged after 18 months storage, but at some higher temperature storage points a change in polymorphic form is reported. Up to 18 months stability data provided at 25°C/60%RH and 30°C/65%RH indicate a stable compound as all parameters including the polymorphic Form I remained almost unchanged.

Updated stability data of 18 months support the re-test period of 18 months.

Drug Product

The development of two strengths of the donepezil hydrochloride film-coated tablet product has been described, the choice of excipients is justified and their functions explained. Pharmaceutical development includes characterisation of donepezil hydrochloride regarding compatibility with the excipients, solubility, water content and polymorphism (Form I).

The 10mg strength is a direct scale up of the 5mg strength tablet. All excipients are compendial grade being Ph.Eur.

The generic product is physico-chemically comparable to the cross reference/brand leader product with regards to both in-vitro dissolution profiles and impurity profiles. The tablet core components are also contained in the reference product.
The drug product specifications cover appropriate parameters for this dosage form including appearance, identification, assay, dissolution, related substances, uniformity of dosage units and microbial quality. The shelf-life specification is similar to that at release. Validations of the analytical methods have been presented giving due consideration to specificity, linearity, range, accuracy, precision, stability of reference and test solution and robustness and for related substances limits of detection and quantitation.

Batch analyses have been performed on 3 batches of tablets of each strength. The batch analysis results show that the finished products meet the specifications proposed and the manufacturing process is capable of producing the product of the desired quality.

The conditions used in the stability studies are according to the ICH stability guideline in that storage conditions of 25°C ± 2°C / 60% ± 5% RH, intermediate storage 30±2°C / 65±5% RH and 40°C ± 2°C / 75% ± 5% have been used. Blister and HDPE marketing packaging have been used for stability batches. The control tests and specifications for drug product are now generally adequate. A shelf-life of 30 months is proposed with no storage restrictions for this stable product.

**Non-clinical aspects**

No new preclinical studies were submitted with this application. This is acceptable as Donepezil Hydrochloride is a well known active ingredient and no new preclinical issues are considered to arise as a result of it inclusion in the proposed product.

**Clinical aspects**

To support the application, the applicant has submitted a single bioequivalence study: a double-blinded, single dose, randomised, 2-way study of crossover design, performed under fasting conditions. The study was performed using the 10mg dose strength.

The company’s clinical expert has provided satisfactory justification for studying the 10mg strength only, rather than both strengths:

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

A review of the PK characteristics of donepezil indicates that absorption is predictable and it appears unlikely that the conclusion of bioequivalence for the lower strength would be any different if the 5mg dose had 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.

**Study design**

A comparative, randomised, two-way, two-period, single dose crossover study performed in fasting subjects. All subjects gave prior informed consent to take part in the study.

Healthy volunteers were randomised to receive a single dose of 10mg orally of either the applicant's test product or the reference product donepezil, following a 10 hour fast.

The randomisation scheme was balanced for sequence and appears random.

Serum drug levels were followed for 240 hours following dosing and the schedule was appropriate for accurate determination of AUC\text{inf} and C\text{max}. The washout period between phases was 28 days.

**Test and reference products**

Reference: Aricept 10mg Film Coated Tablets (Donepezil Hydrochloride) (Eisai Ltd., UK)

Test: Donepezil Hydrochloride 10mg Film Coated Tablets (Donepezil Hydrochloride) (Apotex Inc., Canada.)

**Population(s) studied**

24 healthy fasted state adult volunteers were randomised and 16 completed the study. 8 subjects were withdrawn: three subjects were withdrawn after period 1 due to vomiting within the controlled period; two subjects were withdrawn after period 2 due to vomiting; one subject was withdrawn due to prolongation of the QTc interval on ECG monitoring; and two were withdrawn after period 1 for missing the 240 hours ambulatory visit due to personal reasons. The reasons for these dropouts are satisfactory and the data were handled appropriately according to the study protocol.

10 subjects had plasma Donepezil concentrations greater than the lower limit of quantitation at the start of Period 2. A planned washout period of 28 days, corresponding to 9 – 10 of the documented mean half lives of donepezil, should have been sufficient. The baseline plasma donepezil concentrations were close to the lower limit of quantification and represented less than 1% of the C\text{max} in the second period. These data sets were included for the purposes of pharmacokinetic/statistical evaluation. This is considered satisfactory and there is not assessed to be a deficiency in study design.
Results

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

<table>
<thead>
<tr>
<th></th>
<th>AUC0-t</th>
<th>AUC0-inf</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio</td>
<td>100.7</td>
<td>100.8</td>
<td>103.3</td>
</tr>
<tr>
<td>90% C.I.</td>
<td>97.3-104.3</td>
<td>97.1-104.6</td>
<td>96.9-110.0</td>
</tr>
<tr>
<td>Intra-subject CV%</td>
<td>5.6</td>
<td>6.0</td>
<td>10.2</td>
</tr>
</tbody>
</table>

Six subjects withdrew on account of adverse events (five cases of vomiting, one of ECG out of specification [prolonged QTc interval 456 msec]). All final vital signs (pulse, blood pressure, oral temperature) were within normal limits or judged to be non-clinically serious.

Pharmacokinetic conclusion

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

Pharmacovigilance system

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

As the product is a generic medicinal product containing a well established drug substance, the standard pharmacovigilance system in place is considered appropriate for collection and reporting of pharmacovigilance data, therefore no separate risk management system is proposed.

Benefit-Risk Assessment

The use of Donepezil Hydrochloride is well established. It has recognised efficacy and acceptable safety. With regards to the current application, sufficient clinical information has been submitted which includes adequate review of published clinical data. Overall the risk benefit analysis for Donepezil Hydrochloride 5mg and 10mg Film-coated Tablets is considered favourable and approval is recommended.
Module 6

Steps taken after procedure

There have been no non-confidential changes to the Marketing Authorisations.