

Public Assessment Report

Decentralised

**Donepezil 5mg Film-coated Tablets
Donepezil 10mg Film-coated Tablets**

UK/H/1217/01-02/DC

ICN Polfa Rzeszow S.A.

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Module 1

Product Name	Donepezil hydrochloride 5mg Film-coated Tablets Donepezil hydrochloride 10mg Film-coated Tablets
Type of Application	Standard Abridged Decentralised (Article 10.1)
Active Substance (INN)	Donepezil hydrochloride
Pharmacotherapeutic Classification (ATC)	N06DA02
Pharmaceutical Form and Strength	Tablets, 5mg and 10mg
Procedure Numbers	UK/H/1217/01-02/DC
RMS	UK
CMS	CZ, HU, PL, SK
Start Date	09/07/2007
End Date	29/08/2008
MA Number	PL 19070/0001-2
Name and address of MA holder	ICN Polfa Rzeszow S.A. 2 Przemyslowa Street 35-959 Rzesnow Poland

Module 2

Summary of Product Characteristics

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 tablet:

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

4.2 Posology and method of administration

Adults/Elderly

Treatment is initiated at 5 mg/day (once-a-day dosing). Donepezil hydrochloride should be taken orally, in the evening, just prior to retiring. The 5 mg/day dose should be maintained for at least one month in order to allow the earliest clinical responses to treatment to be assessed and to allow steady-state concentrations of donepezil hydrochloride to be achieved.

Following a one-month clinical assessment of treatment at 5 mg/day, the dose of Donepezil

hydrochloride can be increased to 10 mg/day (once-a-day dosing). The maximum recommended daily dose is 10 mg. Doses greater than 10 mg/day have not been studied in clinical trials.

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Diagnosis should be made according to accepted guidelines (e.g. DSM IV, ICD 10). Therapy with donepezil should only be started if a caregiver is available who will regularly monitor drug intake for the patient. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of donepezil should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to donepezil cannot be predicted.

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

Renal and hepatic impairment

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

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

Children

There is no relevant indication for the use of Donepezil hydrochloride in children.

4.3 Contraindications

Donepezil hydrochloride 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 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:

System Organ Class	Very Common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)
Infections and infestations		Common cold		
Metabolism and nutrition disorders		Anorexia		
Psychiatric disorders		Hallucinations** Agitation** Aggressive behaviour**		
Nervous system disorders		Syncope* Dizziness Insomnia	Seizure*	Extrapyramidal symptoms
Cardiac disorders			Bradycardia	Sino-atrial block Atrioventricular block
Gastrointestinal disorders	Diarrhoea Nausea	Vomiting Abdominal disturbance	Gastrointestinal haemorrhage Gastric and duodenal ulcers	
Hepato-biliary disorders				Liver dysfunction including hepatitis***
Skin and subcutaneous tissue disorders		Rash Pruritis		

Musculoskeletal, connective tissue and bone disorders		Muscle cramps		
Renal and urinary disorders		Urinary incontinence		
General disorders and administration site conditions	Headache	Fatigue 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 sinusal pauses should be considered (see section 4.4)

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

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

4.9 Overdose

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

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

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

donepezil hydrochloride and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-dementia drugs; anticholinesterase.

ATC-code: N06DA02

Donepezil hydrochloride is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain. Donepezil hydrochloride is in vitro over 1000 times more potent an inhibitor of this enzyme than of 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 n=365	Evaluable Population 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 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 C_{max} by 39% (see section 4.2)

5.3 Preclinical safety data

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose Monohydrate

Maize starch

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: 14, 28, 42, 56, 84, 98, 112 film-coated tablets

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

ICN Polfa Rzeszów S.A.

2 Przemysłowa Street,

35-959 Rzeszów, Poland

8 MARKETING AUTHORISATION NUMBER(S)

PL: 19070/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/08/2008

10 DATE OF REVISION OF THE TEXT

29/08/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Donepezil hydrochloride 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Donepezil hydrochloride, 10 mg, film-coated tablet:

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

4.2 Posology and method of administration

Adults/Elderly

Treatment is initiated at 5 mg/day (once-a-day dosing). Donepezil hydrochloride should be taken orally, in the evening, just prior to retiring. The 5 mg/day dose should be maintained for at least one month in order to allow the earliest clinical responses to treatment to be assessed and to allow steady-state concentrations of donepezil hydrochloride to be achieved.

Following a one-month clinical assessment of treatment at 5 mg/day, the dose of Donepezil hydrochloride can be increased to 10 mg/day (once-a-day dosing). The maximum recommended daily dose is 10 mg. Doses greater than 10 mg/day have not been studied in clinical trials.

Treatment should be initiated and supervised by a physician experienced in the diagnosis and treatment of Alzheimer's dementia. Diagnosis should be made according to accepted guidelines (e.g. DSM IV, ICD 10). Therapy with donepezil should only be started if a

caregiver is available who will regularly monitor drug intake for the patient. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of donepezil should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to donepezil cannot be predicted.

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

Renal and hepatic impairment

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

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

Children

There is no relevant indication for the use of Donepezil hydrochloride in children.

4.3 Contraindications

Donepezil hydrochloride 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 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:

System Organ Class	Very Common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)
Infections and infestations		Common cold		
Metabolism and nutrition disorders		Anorexia		
Psychiatric disorders		Hallucinations** Agitation** Aggressive behaviour**		
Nervous system disorders		Syncope* Dizziness Insomnia	Seizure*	Extrapyramidal symptoms
Cardiac disorders			Bradycardia	Sino-atrial block Atrioventricular block
Gastrointestinal disorders	Diarrhoea Nausea	Vomiting Abdominal disturbance	Gastrointestinal haemorrhage Gastric and duodenal ulcers	
Hepato-biliary disorders				Liver dysfunction including hepatitis***
Skin and subcutaneous tissue disorders		Rash Pruritis		
Musculoskeletal, connective tissue and bone disorders		Muscle cramps		
Renal and urinary disorders		Urinary incontinence		

General disorders and administration site conditions	Headache	Fatigue 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 sinusual pauses should be considered (see section 4.4)

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

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

4.9 Overdose

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

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

As in any case of overdose, general supportive measures should be utilised. Tertiary anticholinergics such as atropine may be used as an antidote for Donepezil hydrochloride 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 n=365	Evaluable Population 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 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 C_{max} by 39% (see section 4.2)

5.3 Preclinical safety data

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Lactose Monohydrate

Maize starch

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: 14, 28, 42, 56, 84, 98, 112 film-coated tablets

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
ICN Polfa Rzeszów S.A.
2 Przemysłowa Street,
35-959 Rzeszów, Poland

8 MARKETING AUTHORISATION NUMBER(S)
PL: 19070/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29/08/2008

10 DATE OF REVISION OF THE TEXT

29/08/2008

Module 3

Product Information Leaflet

This product is not to be marketed and has been approved based on EU harmonised texts.

PACKAGE LEAFLET: INFORMATION FOR THE USER

<Product Name>, 5 mg, film-coated tablets 
<Product Name>, 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.
- 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 <Product Name> is and what it is used for
2. Before you take <Product Name>
3. How to take <Product Name>
4. Possible side effects
5. How to store <Product Name>
6. Further information

1. WHAT <PRODUCT NAME> IS AND WHAT IT IS USED FOR

<Product Name> (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 <PRODUCT NAME>

Do not take <Product Name>

You must not take <Product Name> 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 <Product Name>

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 <Product Name>:

- 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 <Product Name>.

Taking <Product Name> with food and drink

<Product Name> 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 <Product Name>.

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 <Product name>

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 <PRODUCT NAME>

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

Take your <Product Name> tablet by mouth with a drink of water at night before you go to bed.

The tablet strength you will take may change depending on the length of time you have been taking the medicine and on what your doctor will recommend. Usually, you will start by taking 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 <Product Name> 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 <Product Name>

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 <Product Name>

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, <Product Name> 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 <Product Name> 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*).

- common cold
- loss of appetite
- vomiting
- abdominal disturbances

- hallucinations
- agitation
- aggressive behaviour
- fainting
- dizziness
- insomnia (difficulty in sleeping)
- accidents
- rash
- itching
- muscle cramp
- urinary incontinence
- fatigue
- pain

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 <PRODUCT NAME>

Do not store above 30 °C.

Keep out of the reach and sight of children.

Do not use <Product Name> 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 <Product Name> contains

The active substance in <Product Name> is donepezil hydrochloride.

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

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

The other ingredients are:

Tablet core:

Lactose Monohydrate, Maize starch, Hydroxypropyl cellulose, Microcrystalline cellulose, Magnesium Stearate

Film-coating:

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

What <Product Name> looks like and contents of the pack

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

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

< Packs: To be completed nationally >

Not all pack sizes may be marketed.

Marketing Authorisation Holder:

<To be completed nationally >

Manufacturer:

<To be completed nationally >

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

<To be completed nationally >

This leaflet was last approved in [MM/YYYY]

Module 4

Labelling

This product is not to be marketed and has been approved based on EU harmonised texts.

PARTICULARS TO APPEAR ON THE CARTON BOX AND THE BLISTER

CARTON

1. NAME OF THE MEDICINAL PRODUCT

<Product Name> 5 mg film-coated tablets 

<Product Name> 10 mg film-coated tablets

Donepezil Hydrochloride

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg of donepezil hydrochloride.

Each tablet contains 10 mg of donepezil hydrochloride.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

<Pack sizes: To be completed nationally>

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

Read the package leaflet before use.

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

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

<To be completed nationally>

12. MARKETING AUTHORISATION NUMBER(S)

<To be completed nationally>

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

<Product Name> 5 mg

<Product Name> 10 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC-PE-PVDC/Aluminium blister strips

1. NAME OF THE MEDICINAL PRODUCT

<Product Name> 5 mg film-coated tablets

<Product Name> 10 mg film-coated tablets

2. NAME OF THE MARKETING AUTHORISATION HOLDER

<To be completed nationally>

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot:

5. OTHER

Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Donepezil 5 and 10 mg film coated tablets, in the symptomatic treatment of mild to moderately severe Alzheimer's dementia, is approvable.

EXECUTIVE SUMMARY

Problem statement

This report evaluates the chemical-pharmaceutical aspects of a decentralised application for Marketing Authorisation, 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 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 S.A.S., France) as the reference. The relevant products in the UK are Aricept 5 and 10mg Film Coated Tablets (Eisai Ltd., UK). The UK acts as RMS.

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 the submitted dossier

These marketing authorisation applications for Donepezil HCl 5 and 10mg film-coated tablets are 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 14.2.1997. Hence the ten year rule is complied with.

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.

Assurance has been provided that the active substance manufacturer operates in accordance with the principles of GMP.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

The chemical-pharmaceutical documentation and Expert Report in relation to donepezil HCl 5 and 10mg film-coated tablets are of sufficient quality in view of the present European regulatory requirements.

The drug substance Donepezil Hydrochloride (rINN) is not the subject of European Pharmacopoeia monograph.

Donepezil has one chiral centre thus it exhibits optical isomerism. Donepezil hydrochloride produced by Jubilant is a racemic mixture.

The manufacture, control tests and specifications for drug substance product are adequately described.

Drug Product

The development of the two strengths of the donepezil hydrochloride film-coated tablet product have been adequately described, the choice of excipients is justified and their functions explained. All excipients are PhEur compendial grade.

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 composition is qualitatively identical to the reference product with film coating being marginally different.

The product specifications cover appropriate parameters for this dosage form and batch analysis has been performed. 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.

Satisfactory stability data obtained under conditions reflecting current requirements have been supplied supporting the shelf-life of 30 months with the following storage condition "Do not store above 30°C."

Non clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of donepezil are well known. As donepezil is a widely used, well-known active substance, no further studies are required and the applicant provides none. An overview based on a review of the literature is, thus, appropriate. No new preclinical issues are considered to arise as a result of inclusion of donepezil in the proposed product.

Clinical aspects

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.

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

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

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.

26 healthy fasting volunteers (20 female and 6 male), aged 24-55 years, were randomised to receive a single dose of 10mg orally of either the applicant's test product or the reference product donepezil.

The randomisation scheme was balanced for sequence and appears random.

Serum drug levels were followed for 288 hours following dosing and the schedule was appropriate for accurate determination of AUC_{inf} and C_{max} . The washout period between phases was 28 days.

Assessor's comment

Satisfactory study protocol.

Test and reference products

Reference: Aricept 10mg Film Coated Tablets (Donepezil Hydrochloride) (Pfizer laboratories, France. Batch No: 6022603. Expiry March 2009)

Test: Donepezil 10mg Film Coated Tablets (Donepezil Hydrochloride) (Specifar S.A., Greece. Batch No: DON10P2. Expiry July 2007)

Assessor's comment:

The comparator product is the EEA product to which essential similarity is claimed and is therefore satisfactory.

Population(s) studied

26 healthy fasted state adult volunteers were randomised and 16 completed the study. 8 subjects were withdrawn: seven subjects were withdrawn after period 1 due to vomiting, one subject was withdrawn after period 2 due to vomiting and two elected to withdraw for personal reasons after period 1. The reasons for these dropouts are satisfactory and the data were handled appropriately according to the study protocol.

Assessor's comment:

No concerns raised.

Analytical methods

Plasma samples were analysed to quantify the concentration of donepezil using a validated LC/MS/MS bioanalytical method. The validation report has been provided. The linearity range for donepezil was 100.48 pg/ml to 25120.00 pg/ml and the lower limit of quantification was 100.48 pg/ml.

Pharmacokinetic Variables**Assessor's comment:**

Conventional bioequivalence criteria.

Statistical methods

ANOVA for AUC, C_{max}. Non-parametric for T_{max}. Analysis of sequence/period effects.

Assessor's comment:

Conventional statistical methods.

Results

Table 1. Pharmacokinetic parameters for parent drug (non-transformed values; arithmetic mean ± SD, t_{max}, median, range). N=16.

Parameters	Test (Donepezil HCl (A))			Reference (Aricept (B))		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC _{0-t} (pg·h/mL)	669298.34	180502.00	26.97	645148.35	159811.15	24.77
AUC _{0-inf} (pg·h/mL)	729673.34	205820.66	28.21	692588.70	182284.55	26.32
C _{max} (pg/mL)	17068.65	2505.61	14.68	16529.08	3568.21	21.59
Residual area (%)	8.06	2.99	37.13	6.46	2.18	33.80
T _{max} (h)	2.90	1.45	49.92	2.74	1.27	46.37
T _{max} * (h)	2.00	2.50	-	2.00	1.66	-
K _{el} (h ⁻¹)	0.0079	0.0015	18.86	0.0085	0.0011	13.41
T _{½el} (h)	91.14	22.51	24.70	82.73	9.79	11.83

* Medians and interquartile ranges are presented.

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

Donepezil HCl (A) vs Aricept (B)			
	AUC _{0-t}	AUC _{0-inf}	C _{max}
Ratio ¹	99.81%	101.36%	104.63%
90 % Geometric C.I. ²	94.95 % to 104.92 %	96.42 % to 106.55 %	95.98 % to 114.05 %
Intra-Subject CV	7.78 %	7.78 %	13.47 %

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

² 90% Geometric Confidence Interval using ln-transformed data

Assessor's comment:

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

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

Pharmacokinetic conclusion

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

Pharmacokinetics

No new data

Pharmacodynamics

No new data

Clinical efficacy

No new data

Clinical safety

No new data

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

The risk management plan for the current application consists of the following:

- Employment of a Qualified person in the EEA for Pharmacovigilance
- Collection and follow up of all suspected adverse reactions
- Submission of Periodic safety update reports (PSURs)
- Reporting of adverse drug reactions
- Monitoring of scientific literature

BENEFIT RISK ASSESSMENT

The benefit – risk assessment for this product is considered to be positive.

Module 6

Steps taken after procedure

No non-confidential alterations have been made to the market authorisations.