Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Donepezil Hydrochloride 5mg Film Coated Tablets
Donepezil Hydrochloride 10mg Film Coated Tablets

UK/H/1145/01-02/DC
UK licence no: PL 04416/0832

Applicant: Sandoz Limited

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Sandoz Limited Marketing Authorisations (licences) for the medicinal products Donepezil Hydrochloride 5mg and 10mg Film Coated Tablets on 25th November 2008. This is a prescription-only medicine used to treat the symptoms of dementia in people diagnosed as having mild to moderately severe Alzheimer's disease.

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

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

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Module 1

Product Name	Donepezil Hydrochloride 5mg Film Coated Tablets Donepezil Hydrochloride 10mg Film Coated Tablets
Type of Application	Generic, Article 10.1
Active Substance	Donepezil Hydrochloride
Form	Film Coated Tablets
Strength	5mg & 10mg
MA Holder	Sandoz Limited, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE, United Kingdom
Reference Member State (RMS)	UK
CMS	Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Spain, Finland, France, Italy, Norway, Poland, Portugal, Romania, Sweden, Slovak Republic and Slovenia
Procedure Number	UK/H/1145/01-02/DC
End of Procedure	18th July 2008

Module 2
Summary of Product Characteristics

The UK Summaries of Product Characteristics (SPC) for Donepezil Hydrochloride 5mg & 10mg Film Coated Tablets are as follows:

1 NAME OF THE MEDICINAL PRODUCT

Donepezil Hydrochloride 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg donepezil hydrochloride.
Excipients:
19 mg lactose/film-coated tablet
0.2 mg soya lecithin/film-coated tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White, round (diameter 7 mm) film-coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

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

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

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

4.3 Contraindications

Hypersensitivity to the active substance, piperidine derivatives, soya, peanut or to any of the excipients.

4.4 Special warnings and precautions for use

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

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

Cardiovascular Conditions:
Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block.
There have been reports of syncope and seizures. In investigating such patients the possibility of heart block or long sinusal pauses should be considered.

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

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

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

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

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

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

Mortality in Vascular Dementia Clinical Trials:
Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients whose dementia appears to be due solely to vascular causes and to exclude patients with Alzheimer's disease. In the first study, the mortality rates were 2/198 (1.0%) on donepezil hydrochloride 5 mg, 5/206 (2.4%) on donepezil hydrochloride 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on donepezil hydrochloride 5 mg and 0/326 (0%) on placebo. The

mortality rate for the three VaD studies combined in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%), however, this difference was not statistically significant. The majority of deaths in patients taking either donepezil hydrochloride or placebo appear to result from various vascular related causes, which could be expected in this elderly population with underlying vascular disease. An analysis of all serious non-fatal and fatal vascular events showed no difference in the rate of occurrence in the donepezil hydrochloride group relative to placebo.

In pooled Alzheimers'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.

Lactose and Glucose:
Donepezil hydrochloride film-coated tablets contain lactose and maize starch (source of glucose). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Donepezil hydrochloride and/or any of its metabolites does 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). The potential risk for humans is unknown.

Donepezil should not be used during pregnancy unless clearly necessary.

Lactation:

Donepezil is excreted in the milk of 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

The most common undesirable effects are diarrhoea, muscle cramps, fatigue, nausea, vomiting, headache 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 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class	Very Common	Common	Uncommon	Rare
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		

System Organ Class	Very Common	Common	Uncommon	Rare
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 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.

Symptoms:
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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-dementia drugs, anticholinesterases
ATC code: N06DA02

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

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 can not be considered to have any effect on the progress of the disease.
Efficacy of treatment of Alzheimer's dementia with donepezil has been investigated in four placebo-controlled trials, 2 trials of 6-month duration and 2 trials of 1-year duration.
In the 6 months clinical trial, an analysis was done at the conclusion of donepezil treatment using a combination of three efficacy criteria: the ADAS-Cog (a measure of cognitive

performance), the Clinician Interview Based Impression of Change with Caregiver Input (a measure of global function) and the Activities of Daily Living Subscale of the Clinical Dementia Rating Scale (a measure of capabilities in community affairs, home and hobbies and personal care).
Patients who fulfilled the criteria listed below were considered treatment responders.
Response =

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

	% Response	
	Intent to Treat Population n = 365	Evaluable Population n = 352
Placebo Group	10%	10%
Donepezil Hydrochloride 5-mg Group	18%*	18%*
Donepezil Hydrochloride 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 ^{14}C-labelled donepezil hydrochloride, approximately 28% of the label remained unrecovered. This suggests that donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

Metabolism/Excretion:
Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of ^{14}C-labelled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil hydrochloride (30%), 6-O-desmethyldonepezil (11% – only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyldonepezil (7%) and the glucuronide conjugate of 5-O-desmethyldonepezil (3%). Approximately 57% of the total administered radioactivity was recovered from the urine (17% as unchanged donepezil), and 14.5% was recovered from the faeces, suggesting biotransformation and urinary excretion as the primary routes of elimination. There is no evidence to suggest enterohepatic recirculation of donepezil hydrochloride and/or any of its metabolites.
Plasma donepezil concentrations decline with a half-life of approximately 70 hours.
Sex, race and smoking history have no clinically significant influence on plasma concentrations of donepezil hydrochloride. The pharmacokinetics of donepezil has not been formally studied in healthy elderly subjects, or in Alzheimer's or vascular dementia patients.

However, mean plasma levels in patients closely agreed with those of young healthy volunteers.
Patients with mild to moderate hepatic impairment had increased donepezil steady state concentrations; mean AUC by 48% and mean C_{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:
Microcrystalline cellulose,
Lactose monohydrate
Maize starch
Magnesium stearate

Tablet coat:
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Macrogol 3350
Soya lecithin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6 months after first opening of the HDPE-bottle

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/Aluminium blister
Pack sizes of 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100, 100x1 or 120 film-coated tablets

HDPE-bottle with a PP- or a HDPE-screw cap
Pack size of 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
37 Woolmer Way
Bordon
Hampshire
GU35 9QE

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0832

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/11/2008

10 DATE OF REVISION OF THE TEXT

21/11/2008

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Donepezil Hydrochloride 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg donepezil hydrochloride.

Excipients:
38 mg lactose/film-coated tablet
0.4 mg soya lecithin/film-coated tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Yellow, round (diameter 9 mm) film-coated tablet with score line. The film-coated tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

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

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

Children and adolescents:

Donepezil is not recommended for use in children and adolescents below 18 years of age.

4.3 Contraindications

Hypersensitivity to the active substance, piperidine derivatives, soya, peanut or to any of the excipients.

4.4 Special warnings and precautions for use

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

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

Cardiovascular Conditions:
Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block.
There have been reports of syncope and seizures. In investigating such patients the possibility of heart block or long sinusal pauses should be considered.

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

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

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

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

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

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

Mortality in Vascular Dementia Clinical Trials:
Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients whose dementia appears to be due solely to vascular causes and to exclude patients with Alzheimer's disease. In the first study, the mortality rates were 2/198 (1.0%) on donepezil hydrochloride 5 mg, 5/206 (2.4%) on donepezil hydrochloride 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on donepezil hydrochloride 5 mg and 0/326 (0%) on placebo. The mortality rate for the three VaD studies combined in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%), however, this difference was

not statistically significant. The majority of deaths in patients taking either donepezil hydrochloride or placebo appear to result from various vascular related causes, which could be expected in this elderly population with underlying vascular disease. An analysis of all serious non-fatal and fatal vascular events showed no difference in the rate of occurrence in the donepezil hydrochloride group relative to placebo.

In pooled Alzheimers'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.

Lactose and Glucose:
Donepezil hydrochloride film-coated tablets contain lactose and maize starch (source of glucose). Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Donepezil hydrochloride and/or any of its metabolites does 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). The potential risk for humans is unknown.

Donepezil should not be used during pregnancy unless clearly necessary.

Lactation:

Donepezil is excreted in the milk of 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

The most common undesirable effects are diarrhoea, muscle cramps, fatigue, nausea, vomiting, headache 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 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000), not known (cannot be estimated from the available data)

System Organ Class	Very Common	Common	Uncommon	Rare
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 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.

Symptoms:
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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-dementia drugs, anticholinesterases
ATC code: N06DA02

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

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 can not be considered to have any effect on the progress of the disease.
Efficacy of treatment of Alzheimer’s dementia with donepezil has been investigated in four placebo-controlled trials, 2 trials of 6-month duration and 2 trials of 1-year duration.
In the 6 months clinical trial, an analysis was done at the conclusion of donepezil treatment using a combination of three efficacy criteria: the ADAS-Cog (a measure of cognitive performance), the Clinician Interview Based Impression of Change with Caregiver Input (a measure of global function) and the Activities of Daily Living Subscale of the Clinical Dementia Rating Scale (a measure of capabilities in community affairs, home and hobbies and personal care).
Patients who fulfilled the criteria listed below were considered treatment responders.
Response =

Improvement of ADAS-Cog of at least 4 points
No deterioration of CIBIC

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

	% Response	
	Intent to Treat Population n = 365	Evaluable Population n = 352
Placebo Group	10%	10%
Donepezil Hydrochloride 5-mg Group	18%*	18%*
Donepezil Hydrochloride 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 ^{14}C-labelled donepezil hydrochloride, approximately 28% of the label remained unrecovered. This suggests that donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

Metabolism/Excretion:
Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of ^{14}C-labelled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil hydrochloride (30%), 6-O-desmethyldonepezil (11% – only metabolite that exhibits activity similar to donepezil hydrochloride), donepezil-cis-N-oxide (9%), 5-O-desmethyldonepezil (7%) and the glucuronide conjugate of 5-O-desmethyldonepezil (3%). Approximately 57% of the total administered radioactivity was recovered from the urine (17% as unchanged donepezil), and 14.5% was recovered from the faeces, suggesting biotransformation and urinary excretion as the primary routes of elimination. There is no evidence to suggest enterohepatic recirculation of donepezil hydrochloride and/or any of its metabolites.
Plasma donepezil concentrations decline with a half-life of approximately 70 hours.
Sex, race and smoking history have no clinically significant influence on plasma concentrations of donepezil hydrochloride. The pharmacokinetics of donepezil has not been formally studied in healthy elderly subjects, or in Alzheimer's or vascular dementia patients. However, mean plasma levels in patients closely agreed with those of young healthy volunteers.
Patients with mild to moderate hepatic impairment had increased donepezil steady state concentrations; mean AUC by 48% and mean C_{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:
Microcrystalline cellulose,
Lactose monohydrate
Maize starch
Magnesium stearate

Tablet coat:
Polyvinyl alcohol
Talc
Titanium dioxide (E171)
Macrogol 3350
Soya lecithin
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months
6 months after first opening of the HDPE-bottle

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC/Aluminium blister
Pack sizes of 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100, 100x1 or 120 film-coated tablets

HDPE-bottle with a PP- or a HDPE-screw cap
Pack size of 100 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
37 Woolmer Way
Bordon
Hampshire
Gu35 9QE

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/0833

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/11/2008

10 DATE OF REVISION OF THE TEXT

21/11/2008

Module 3
Patient Information Leaflet

Package leaflet: Information for the user SZ00000LT000

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:

SANDOZ

1 What Donepezil hydrochloride is and what it is used for

Donepezil hydrochloride belongs to a group of medicines called acetylcholinesterase inhibitors.

Donepezil hydrochloride is used to treat the **symptoms of dementia** in people diagnosed as having mild to moderately severe **Alzheimer's disease.**

2 Before you take Donepezil hydrochloride

Do not take Donepezil hydrochloride
if you are **allergic** (hypersensitive) to
- donepezil hydrochloride or
- piperidine derivatives, which are similar substances to donepezil, or
- soya, peanut or any of the other ingredients of Donepezil hydrochloride as listed under "6. Further information".

Take special care with Donepezil hydrochloride
if any of the following concerns you, you or your caretaker should **inform your doctor or pharmacist.**
- stomach or duodenal ulcers.
- seizures or shaking and uncontrollable movement especially of the face and tongue but also of the limbs Donepezil may have the potential to cause seizures.
- heart disease, for example sick sinus syndrome or other supraventricular heart conduction disorders and slow heart beat.
  Donepezil may slow down your heart rate.
- asthma or other long term lung disease.
- liver problems or hepatitis.
- difficulty passing urine.
- planned operation requirering a general anaesthetic. Please inform the anaesthetist because donepezil may exaggerate muscle relaxation during anaesthesia.
- ongoing treatment with certain pain killers which also reduce inflammation, so called nonsteroidal anti-inflammatory drugs such as acetylsalicylic acid, diclofenac or ibuprofen.

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

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.

The following medicines can influence Donepezil hydrochloride or be influenced by Donepezil hydrochloride:
- **erythromycin**, an antibiotic
- **ketoconazole** and **itraconazole**, medicines to treat fungal infections
- **succinylcholine**, a muscle relaxant
- **fluoxetine**, an antidepressant of the so called selective serotonin reuptake inhibitors
- **phenytoin** and **carbamazepine**, medicines to treat epilepsy
- **rifampicin**, used to treat tuberculosis
- **quinidine** and **beta-blockers**, medicines to treat certain heart conditions
- general **anaesthetics** from the succinylcholine type
- other medicines acting as **neuro-muscular blocking agents** or as **cholinergic agonists** or having **anticholinergic activity**

Taking Donepezil hydrochloride with food and drink
Do not drink any alcohol during treatment with Donepezil hydrochloride as this may reduce the medicine's effectiveness.

Pregnancy and breast-feeding
- **Do not take** Donepezil hydrochloride if you are pregnant unless your doctor decides that it is clearly necessary. Inform your doctor immediately if you are pregnant or think you may be pregnant.
- **Do not breast-feed** while taking Donepezil hydrochloride.

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

Driving and using machines
Alzheimer's disease may impair your ability to drive or operate machines. Do not perform these activities unless your doctor has confirmed that this is safe.
This medicine can cause fatigue, dizziness and muscle cramps particularly during the beginning of therapy and dose increase. If affected you must not drive or operate machines.

Important information about some of the ingredients of Donepezil hydrochloride
Donepezil hydrochloride contains lactose and maize starch (source of glucose).
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3 How to take Donepezil hydrochloride

Always take Donepezil hydrochloride exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
The usual dose is:

Adults and elderly patients
Donepezil Hydrochloride 5 mg Film-coated Tablets:
- **Starting dose:** 1 film-coated tablet every night
- **After one month:** possible increase to 2 film-coated tablets every night.
- **Maximum dose:** 2 film-coated tablets every night

Donepezil Hydrochloride 10 mg Film-coated Tablets:
- **Starting dose:** ½ film-coated tablet every night
- **After one month:** possible increase to 1 film-coated tablet every night.
- **Maximum dose:** 1 film-coated tablet every night

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

Patients with kidney dysfunction
You can take the usual dose as described above. No adjustment is required.

Patients with mild to moderate liver dysfunction
Your doctor will check your tolerance to Donepezil hydrochloride before increasing the dose.

Patients with severe liver dysfunction
Your doctor will decide if Donepezil hydrochloride is suitable for you.

Method of administration
Take your film-coated tablets at night before you go to bed, independently from meals. Swallow the film-coated tablets with a glass of water.

Duration of use
Your doctor will decide the duration of treatment. Regular check-ups for treatment review and symptom assessment are necessary.

If you take more Donepezil hydrochloride than you should
If you have taken too much of Donepezil hydrochloride **contact your doctor or a hospital immediately.** Take the film-coated tablets, this leaflet and/or the carton with you to show the doctor what you have taken.

Continued on the next page >>

Signs of an overdose needing medical care straight away are:
- severe nausea
- vomiting
- salivation
- sweating
- slow heart beat
- low blood pressure
- respiratory depression
- collapse and convulsions
- increasing muscle weakness.

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

If you stop taking Donepezil hydrochloride
Do not stop taking the film-coated tablets unless instructed by your doctor. Positive treatment results may gradually diminish if treatment is stopped.

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 hydrochloride can cause side effects, although not everybody gets them. These disappear in most cases without having to stop treatment.

Reported side effects listed according to the frequencies are:
Very common, occurs in more than 1 per 10 users:
- diarrhoea
- nausea
- headache

Common, occurs in 1 to 10 per 100 users:
- common cold
- loss of appetite
- hallucinations, agitation, aggressive behaviour
  Your doctor may reduce the dose or stop treatment with Donepezil hydrochloride in such a case.
- fainting, dizziness, difficulty sleeping
- vomiting, abdominal disturbance
- rash, itching
- muscle cramps
- inability to retain urine
- fatigue, pain
- accident

Uncommon, occurs in 1 to 10 per 1,000 users:
- seizure
- slow heart beat
- gastrointestinal bleeding, stomach and duodenal ulcers
- minor increase in blood levels of the enzyme creatine kinase

Rare, occurs in 1 to 10 per 10,000 users:
- shaking, stiffness or uncontrollable movement especially of the face and tongue but also of the limbs
- heart block, known assino-atrial block or atrioventricular block
- liver disorders including hepatitis
  Your doctor may stop treatment with Donepezil hydrochloride in such a case.

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

5 How to store Donepezil hydrochloride

Keep out of the reach and sight of children.

Do not use Donepezil hydrochloride after the expiry date which is stated on the carton and blister or on the label of the plastic-bottle. The expiry date refers to the last day of that month.

Do not store above 25°C.

Do not use Donepezil hydrochloride after 6 months have elapsed from first opening of the plastic-bottle.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 Further information

What Donepezil hydrochloride contains
The active substance is donepezil hydrochloride.
Each film-coated tablet contains 5 mg of donepezil hydrochloride.
Each film-coated tablet contains 10 mg of donepezil hydrochloride.

The other ingredients are:
Tablet core:
Microcrystalline cellulose, Lactose monohydrate, Maize starch, Magnesium stearate

Tablet coat:
5 mg:
Polyvinyl alcohol, Talc, Titanium dioxide (E171), Macrogol 3350, Soya lecithin

10 mg:
Polyvinyl alcohol, Talc, Titanium dioxide (E171), Macrogol 3350, Soya lecithin, Iron oxide yellow (E172)

What Donepezil hydrochloride looks like and contents of the pack
Donepezil Hydrochloride 5 mg Film-coated Tablets are white and round (diameter 7 mm).

Donepezil Hydrochloride 10 mg Film-coated Tablets are yellow and round (diameter 9 mm) with score line. They can be divided into equal halves.

Donepezil hydrochloride film-coated tablets are available in
- blisters
  Pack sizes of 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100, 100x1 or 120 film-coated tablets
- plastic-bottles with a screw cap
  Pack sizes of 100 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Sandoz Ltd, 37 Woolmer Way, Bordon, Hampshire, GU35 9QE

Manufacturer
Salutas Pharma GmbH, Otto-von-Guericke-Allee 1, 39179 Barleben, Germany *or*
Salutas Pharma GmbH, Dieselstrasse 5, 70839 Gerlingen, Germany *or*
Lek Pharmaceuticals d.d., Verovskova 57, 1526 Ljubljana, Slovenia *or*
LEK S.A., ul. Domaniewska 50 C, 02-672 Warsaw, Poland *or*
Sandoz S.R.L., Str. Livezeni nr. 7A, 540472 Targu-Mures, Romania

This medicinal product is authorised in the Member States of the EEA under the following names:

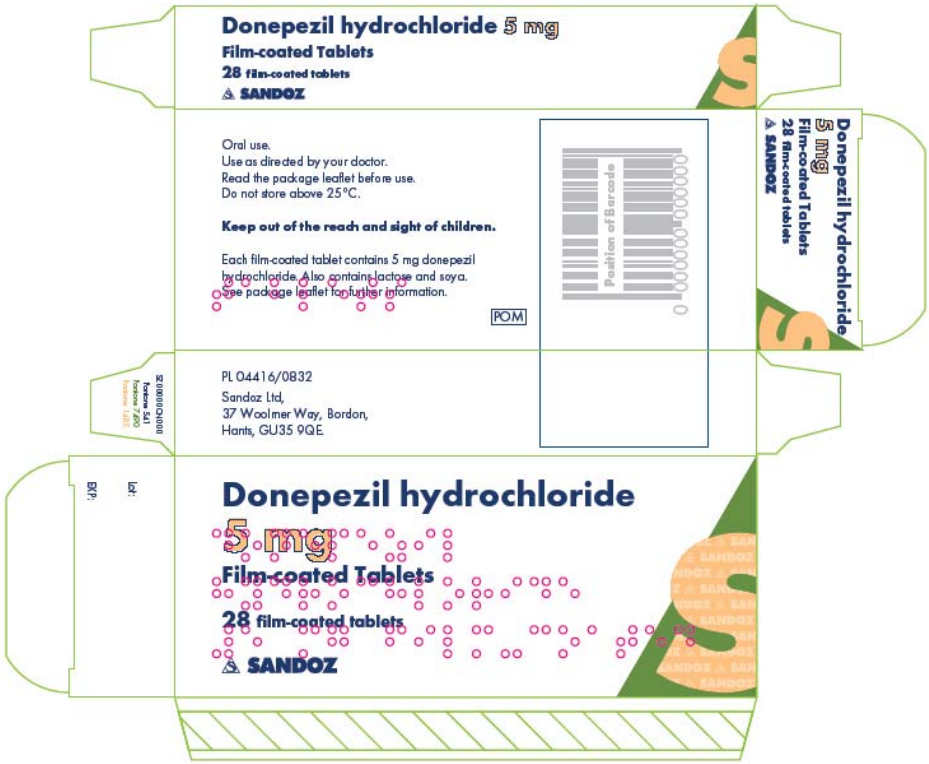
Austria:	Donepezil HCl Sandoz 5mg – Filmtabletten Donepezil HCl Sandoz 10mg – Filmtabletten
Belgium:	Donepezil Sandoz 5 mg filmomhulde tabletten Donepezil Sandoz 10 mg filmomhulde tabletten
Czech Republic:	Donepezil Sandoz 5mg potahované tablety Donepezil Sandoz 10mg potahované tablety
Denmark:	Aripezil
Finland:	Donepezil Sandoz 5 mg tabletti, kalvopäällysteinen Donepezil Sandoz 10 mg tabletti, kalvopäällysteinen
France:	DONEPEZIL Sandoz 5 mg, comprimé pelliculé DONEPEZIL Sandoz 10 mg, comprimé pelliculé
Germany:	Donepezil-HCl Sandoz 5 mg Filmtabletten Donepezil-HCl Sandoz 10 mg Filmtabletten
Greece:	Donepezil/ Sandoz
Italy:	DONEPEZIL SANDOZ 5 mg compresse rivestite con film DONEPEZIL SANDOZ 10 mg compresse rivestite con film
Norway:	Donepezil Sandoz
Poland:	DoneSAN
Portugal:	DONEPEZILO SANDOZ
Romania:	Zildon 5 mg comprimate filmate Zildon 10 mg comprimate filmate
Slovakia:	Donepezil Sandoz 5 mg filmom obalené tablety Donepezil Sandoz 10 mg filmom obalené tablety
Slovenia:	Donepezil Lek 5 mg filmsko obložene tablete Donepezil Lek 10 mg filmsko obložene tablete
Spain:	Donepezilo Sandoz 5 mg comprimidos recubiertos con película EFG Donepezilo Sandoz 10 mg comprimidos recubiertos con película EFG
Sweden:	Donepezil Sandoz
United Kingdom:	Donepezil Hydrochloride 5 mg Film-coated Tablets Donepezil Hydrochloride 10 mg Film-coated Tablets

This leaflet was last approved in 10/2008 *(to be amended after approval).*

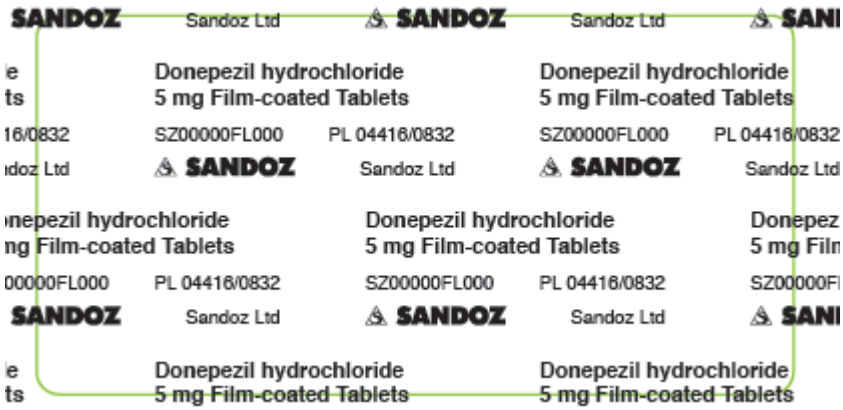
SZ00000LT000

Module 4
Labelling

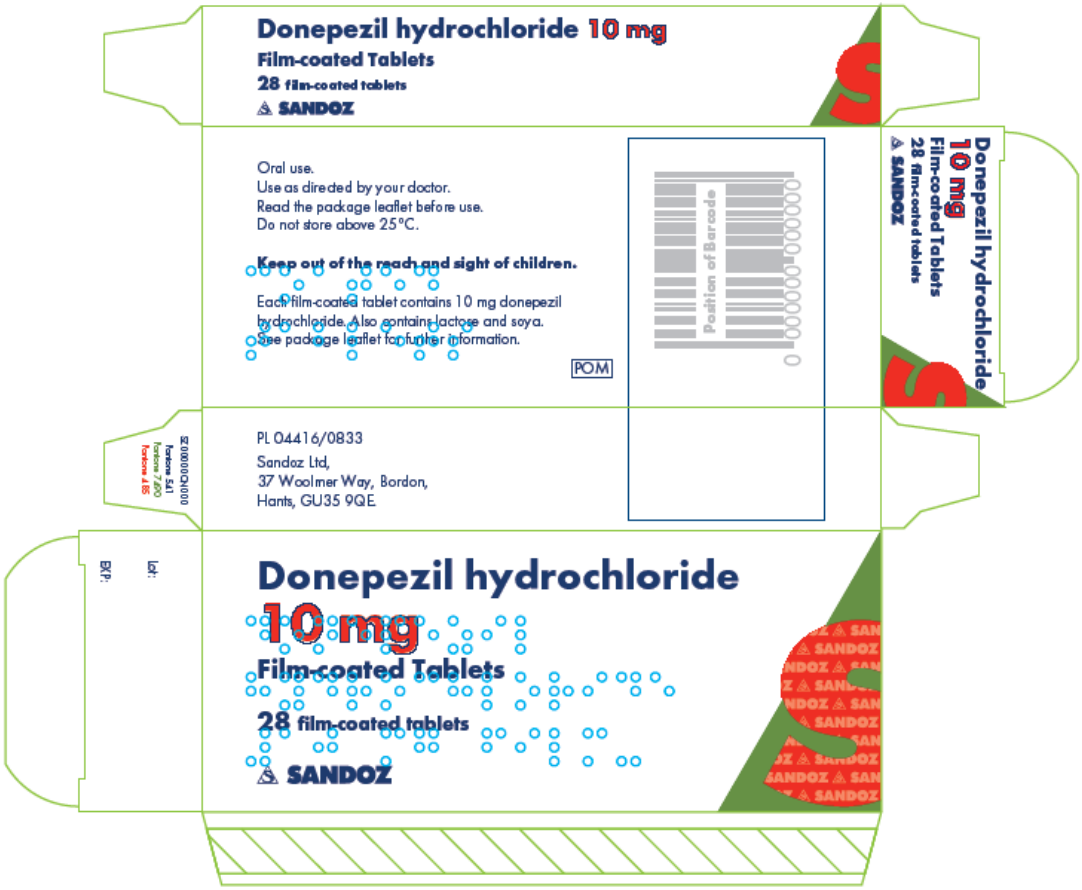
Donepezil Hydrochloride 5mg Film Coated Tablets
Carton



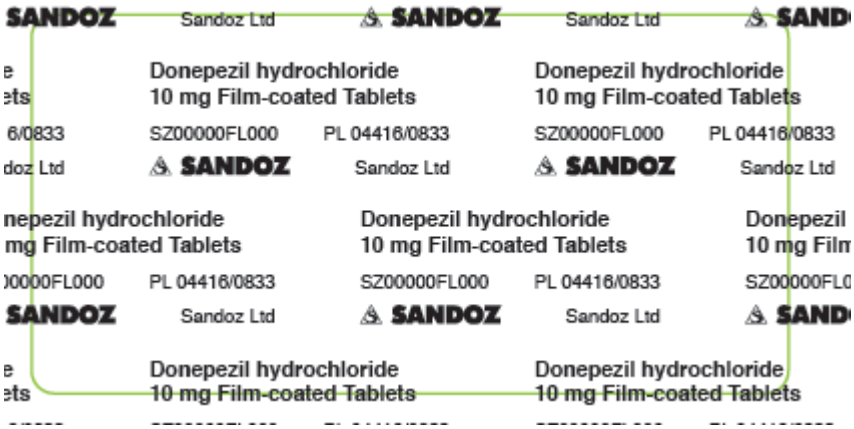
Blister Foil



Donepezil Hydrochloride 10mg Film Coated Tablets
Carton



Blister foil



Module 5
Scientific discussion during initial procedure

INTRODUCTION

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 5mg and 10mg film-coated tablets in the treatment of mild to moderately severe Alzheimers dementia is approvable.

These applications were submitted under Article 10.1 of Directive 2001/83 EC (as amended), for Donepezil hydrochloride 5mg Film Coated Tablets and Donepezil hydrochloride 10mg Film Coated Tablets. They have been shown to be generic medicinal products of the originator products Aricept 5mg and 10mg Tablets (Marketing Authorisation Holder: Eisai Limited, UK) which were granted licences on 14th February 1997 in the UK.

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

No new preclinical studies were conducted, which is acceptable given that the applications were based on essential similarity to products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59

of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Donepezil Hydrochloride 5mg Film-Coated Tablets Donepezil Hydrochloride 10mg Film-Coated Tablets
Name(s) of the active substance(s) (INN)	Donepezil hydrochloride
Pharmacotherapeutic classification (ATC code)	N06D A02: anticholinesterase
Pharmaceutical form and strength(s)	5mg and 10mg Film Coated Tablets
Reference numbers for the Mutual Recognition Procedure	UK/H/1145/01-02/DC
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Czech Republic, Germany, Denmark, Greece, Spain, Finland, France, Italy, Norway, Poland, Portugal, Romania, Sweden, Slovak Republic and Slovenia
Marketing Authorisation Number(s)	PL 04416/0832-3
Name and address of the authorisation holder	Sandoz Limited, 37 WoolmerWay, Bordon, Hampshire, GU35 9QE, UK

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

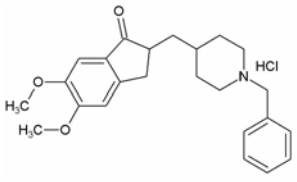
S. Active substance

Nomenclature:

INN: Donepezil hydrochloride

Chemical name: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1H-inden-1-one, hydrochloride

Structure:



Molecular formula

$C_{24}H_{30}ClNO_3$

Molecular weight

415.95 g/mol

General Properties

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

Solubility

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

Polymorphism:

Donepezil Hydrochloride is known to exist in different polymorphic forms including hydrates, anhydrates, crystalline and amorphous form.

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

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

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

Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for standards used by the active substance manufacturer during validation studies.

Appropriate stability data have been generated for drug substance stored in the same immediate packaging as the commercial packaging. The data demonstrates the stability of the drug substance and supports an appropriate retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

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

The tablet coating contains: polyvinyl alcohol, talc, titanium dioxide (E171), macrogol 3350, soya lecithin and (iron oxide yellow (E172)- only present in 10mg strength). All the ingredients within the tablets coating comply with their relevant Ph Eur monographs with the exception of lecithin which complies with USNF (US National Formulary) and JP (Japanese Pharmacopeia).

Appropriate justification for the inclusion of each excipient has been provided.

Satisfactory certificates of analysis have been provided for all excipients.

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

Pharmaceutical development

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

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

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

Dissolution and impurity profiles

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

Manufacturing Process

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

Finished Product Specification
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container-Closure System
Donepezil hydrochloride tablets are packaged either in clear polyvinyl chloride (PVC)/aluminium blister packs or in high density polyethylene (HDPE) containers with a (polypropylene) PP or HDPE screw cap containing desiccant. Blister pack presentation is available in pack sizes of 7, 10, 14, 28, 30, 50, 56, 60, 84, 90, 98, 100, 100x1 or 120 film-coated tablets and the bottle presentation is available in pack sizes of 100 tablets. All primary product packaging complies with EU legislation regarding contact with food.

Stability of the product
Stability studies have been performed on the six batches of 5mg strength and seven batches of 10mg strength. All batches are packaged in the proposed commercial packaging. Stability testing is performed according to the relevant ICH guidelines.
Based on the results of the stability studies, the applicant has proposed a shelf life of 18 months and 6months after first opening of the HDPE bottle, with storage conditions of “Do not store above 25°C”. These are acceptable.

SPC, PIL, Labels
The SPC, PIL and Labels are pharmaceutically acceptable. A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion
The grant of marketing authorisations is recommended.

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

III.3 CLINICAL ASPECTS

Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier. For more details, the reader should refer to the company's clinical overview and summary and to the clinical file.

The clinical overview dated 14 May 2007 has been written by a suitably qualified person with relevant experience in the pharmaceutical industry. The report refers to 66 publications up to 2006.

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

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

Biowaiver
The multiple strengths exemption criterion for linear pharmacokinetics over the therapeutic range is met.

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

a. The pharmacokinetics are linear

b. The qualitative composition is the same

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

d. The dissolution rate of the highest strength of the test product in-vitro is similar to that of the lower strength, and the dissolution rate of both of the strengths of the test product in vitro is similar to the dissolution rates of the corresponding strengths of the reference product.

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

In conclusion the use of the 10mg strength only for the bioequivalence studies has been adequately justified and the results of Study 2006-24-FTA-1 with the 10mg formulation can be extrapolated to other strength 5mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

Pharmacokinetic studies
Study 2006-24-FTA-1

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

Healthy, fasting, male volunteers, aged 23-44 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 72 hours following dosing and the schedule was appropriate for accurate determination of AUC_{0-72} and C_{max}. The washout period between phases was sufficiently long at 21 days.

Test and reference products

Reference: Aricept 10mg Film Coated Tablets (Donepezil Hydrochloride) (Eisai GmbH, Germany.)

Test : Donepezil 10mg Film Coated Tablets (Donepezil Hydrochloride) (HEXAL AG, Germany)

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 lower limit of quantification was 0.250 ng/ml for donepezil and 50.0 pg/ml for 6-O-desmethyldonepezil.

Statistical methods

ANOVA for AUC_{0-72}, $C_{max.}$ Non-parametric for T_{max}. Analysis of sequence/period effects.

Results

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

Parameter	TEST				REFERENCE				F (treatment)	p
	Geometric LS Mean	Arithmetic Mean	S.D.	C.V.	Geometric LS Mean	Arithmetic Mean	S.D.	C.V.		
C_{max} (ng/mL)	15.607	16.235	4.593	28.3	16.463	17.210	5.514	32.0	1.96	N.S.
T_{max} (hours)*	[illegible]	3.50	0.88	23.1	[illegible]	3.00	0.97	30.6	102	<0.005
AUC_{0-72} (ng·h/mL)	413.494	433.494	131.939	30.4	414.692	432.908	125.612	29.0	0.05	N.S.

n=17

* median is presented and test statistic of treatment effect is based on Wilcoxon's.

N.S. = Not Significant (p>0.05)

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

PARAMETER*	RATIO (%)	90% CONFIDENCE LIMITS (%)		INTRA-SUBJECT C.V. (%)
		LOWER	UPPER	
C_{max}	94.80	89.42	100.50	9.65
AUC_{0-72}	99.71	95.25	104.38	7.56

* units are ng/mL for C_{max} and ng·h/mL for AUC_{0-72}.

Table 3. Pharmacokinetic parameters for 6-O-desmethyldonepezil (non-transformed values; arithmetic mean ± SD, t_{max}, median, range).

Parameter	TEST				REFERENCE				F (treatment)	P
	Geometric LS Mean	Arithmetic Mean	S.D.	C.V.	Geometric LS Mean	Arithmetic Mean	S.D.	C.V.		
C_{max} (pg/mL)	73.2	74.9	14.6	19.5	74.7	79.5	29.9	37.6	0.29	N.S.
T_{max} (hours)*	[illegible]	4.00	0.95	24.0	[illegible]	3.75	2.46	56.2	14.5	N.S.
AUC_{0-72} (pg·h/mL)	261.9	405.1	262.0	64.7	187.9	365.6	358.7	98.1	0.06	N.S.

* median is presented and test statistic of treatment effect is based on Wilcoxon's.
N.S. = Not Significant (p>0.05)

Table 4. Pharmacokinetic parameters for 6-O-desmethyldonepezil (log-transformed values).

PARAMETER*	RATIO (%)	90% CONFIDENCE LIMITS (%)		INTRA-SUBJECT C.V. (%)
		LOWER	UPPER	
C_{max}	98.07	79.76	120.57	19.36
AUC_{0-72}	139.37	66.59	291.66	77.47

* units are pg/mL for C_{max} and pg·h/mL for AUC_{0-72}.

Assessor's comment:
These results are within conventional bioequivalence criteria, with 90% confidence intervals between 80-125% for the parent drug only. It is noted that the data for the 6-O-Desmethyl metabolite are not within conventional bioequivalence acceptance criteria. Displaying activity equal to that of the parent drug, this metabolite is to be found in concentrations up to 20% that of the parent drug. There is no evidence to suggest entero-hepatic recycling or accumulation.

From the data presented, there would seem to be two possible explanations for what is seen:

1. Statistical - 90% CIs are very wide and include unity so there may be no formulation difference at all.

2. True formulation difference. The estimated 5% lower Cmax for the test product indicates a slightly slower drug delivery, resulting in a greater proportion being metabolised pre-systemically into the active metabolite, resulting in bioinequivalence for the metabolite.

Either way, the active metabolite cannot be considered to contribute greatly to the activity of this product. There have been a number of other European procedures for donepezil products whereby the metabolites have not been assayed at all. Overall, it is considered that this product fulfils conventional bioequivalence acceptance criteria.

Pharmacokinetic conclusion

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

The results of Study 2006-24-FTA-1 with the 10mg formulation can be extrapolated to the other strength, 5mg, according to conditions in Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, section 5.4.

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

Benefit-Risk Assessment
The application contains an adequate review of published clinical data and the bioequivalence has been shown. Approval is recommended from the clinical point of view.

SUMMARY OF PRODUCT CHARACTERISTICS
The SPCs are in line with those of the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET
The PIL is satisfactory.

LABELLING
Medically satisfactory.

DISCUSSION
The application contains an adequate review of published clinical data.
Bioequivalence has been demonstrated for 10mg tablets. The results could be extrapolated to 5mg tablets.

The clinical safety and efficacy of donepezil hydrochloride is well established as it has been used extensively in clinical practice.

The SPCs are in line with those for the reference products and are satisfactory. The PIL and labelling are medically satisfactory.

CONCLUSIONS
The grant of marketing authorisations is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant's Donepezil hydrochloride 10mg Film-Coated Tablets and the reference product Aricept 10mg Tablets. (Eisai Limited). As these products meet the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to the 5 mg strength tablets.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with donepezil hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome