Public Assessment Report

Mutual Recognition Procedure

Aricept Evess 5mg Orodispersible Tablets
Aricept Evess 10mg Orodispersible Tablets

UK/H/182/03-04

UK licence no: PL 10555/0019-20

Eisai Limited

LAY SUMMARY

The MHRA has granted Eisai Limited Marketing Authorisations (licenses) for the medicinal products Aricept Evess 5mg and 10mg Orodispersible Tablets (PL 10555/0019-20).

These are prescription only medicines (POM) for the treatment of mild to moderately severe Alzheimer's dementia.

Aricept Evess 5mg and 10mg Orodispersible Tablets contain the active ingredient donepezil hydrochloride. 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 Aricept Evess 5mg and 10mg Orodispersible Tablets outweighs the risks, hence Marketing Authorisations were granted.

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Module 1

Product Name	Aricept Evess 5mg orodispersible Tablets Aricept Evess 10mg orodispersible Tablets
Type of Application	Full Dossier, Article 8.3(i)
Active Substance	Donepezil Hydrochloride
Form	Tablet
Strength	5mg and 10mg Tablets
MA Holder	Eisai Limited, Hammersmith International Centre, 3 Shortlands, Hammersmith London W6 8EE United Kingdom
RMS	UK
CMS	Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Portugal, Sweden
Procedure Number	UK/H/182/03-04
Timetable	Day 90 - 21st December 2005

Module 2

Summary of Product Characteristics

European Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Aricept Evess 5 mg orodispersible tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

orodispersible tablet.
White tablet embossed with "5" on one side and "Aricept" on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Aricept Evess 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). Aricept Evess should be taken orally, in the evening, just prior to retiring. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water,

according to patient preference. 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 Aricept Evess 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 Aricept 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:
Aricept is not recommended for use in children.

4.3. Contraindications

Aricept 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 Aricept in patients with severe dementia, other types of dementia or other types of memory impairment (e.g., age-related cognitive decline), has not been investigated.

Anaesthesia: Aricept, 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 Aricept 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 Aricept, 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 Aricept 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.

4.5. Interactions 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 that 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.
Aricept should not be used during pregnancy unless clearly necessary.

Lactation:

Donepezil is excreted in the milk of rat. 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 adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as:
common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100) and rare (>1/10,000, <1/1,000).

System Organ Class	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 Vomiting Nausea 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 Aricept 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 Aricept 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 (haemodialysis, peritoneal dialysis, or haemofiltration).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

The 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.

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

Efficacy of treatment of Alzheimer's Dementia with Aricept 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	Evaluable Population
	n = 365	n = 352
Placebo Group	10%	10%
Aricept 5-mg Group	18%*	18%*
Aricept 10-mg Group	21%*	22%**

*$p < 0.05$
**$p < 0.01$

Aricept 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

Mannitol
Colloidal anhydrous Silica
κ-Carrageenan
Polyvinyl alcohol

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Blister (PVC/PVdC/PE/PVdC/PVC/Aluminium foil)
Pack sizes: 7, 28, 30, 56, 60, 98 or 120 tablets

Not all pack sizes may be marketed.

6.6. Special precautions for disposal of a used medicinal product or waste derived from such medicinal product and other handling of the product.

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aricept Evess 10 mg orodispersible tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

orodispersible tablet.
Yellow tablet embossed with "10" on one side and "Aricept" on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Aricept Evess 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). Aricept Evess should be taken orally, in the evening, just prior to retiring. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference. 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 Aricept Evess 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 Aricept 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:
Aricept is not recommended for use in children.

4.3. Contraindications

Aricept 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 Aricept in patients with severe dementia, other types of dementia or other types of memory impairment (e.g., age-related cognitive decline), has not been investigated.

Anaesthesia: Aricept, 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 Aricept 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 Aricept, 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 Aricept 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.

4.5. Interactions 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 that 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.
Aricept should not be used during pregnancy unless clearly necessary.

Lactation:

Donepezil is excreted in the milk of rat. 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 adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.

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

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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 Vomiting Nausea 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 Aricept 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 Aricept 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 (haemodialysis, peritoneal dialysis, or haemofiltration).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

The 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.

<u>Alzheimer's Dementia</u>

In patients with Alzheimer's Dementia participating in clinical trials, administration of single daily doses of 5 mg or 10 mg of Aricept 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 that examines selected aspects of cognition. The potential for donepezil hydrochloride to alter the course of the underlying neuropathology has not been studied. Thus, Aricept can not be considered to have any effect on the progress of the disease.

Efficacy of treatment of Alzheimer's Dementia with Aricept 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%
Aricept 5-mg Group	18%*	18%*
Aricept 10-mg Group	21%*	22%**

*$p < 0.05$
**$p < 0.01$

Aricept 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

Mannitol
Colloidal anhydrous Silica
κ-Carrageenan
Polyvinyl alcohol
Ferric oxide (yellow) "E172"

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5. Nature and contents of container

Blister (PVC/PVdC/PE/PVdC/PVC/Aluminium foil)
Pack sizes: 7, 28, 30, 56, 60, 98 or 120 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste derived from such medicinal product and other handling of the product.

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Module 3:
Product Information Leaflet

PL 0555/6020.

Service développement Pfizer Amboise

ARICEPT Evess UK
MOCK080D (version 3) / Création
Notice bobine
Format : 135 x 315 mm
Recto : 4a + spot / Verso : 4b

COULEUR
Cyan
Magenta
Noir

APPROVAL
Signature/Date

Patient Information Leaflet

Aricept® Evess 5mg tablets
Aricept® Evess 10mg tablets

(Donepezil Hydrochloride Orodispersible Tablets)

Please read this leaflet

You and your caregiver should read this leaflet carefully before you start to use your medicine. It contains a summary of the information available on your medicine. If after reading this you do not understand or have any questions, ask your doctor or pharmacist (chemist). Pharmaceutical companies are not allowed to answer questions from patients about their medicines.

Keep this leaflet. You may want to read it again.

What is in your tablets?

The active ingredient in Aricept Evess is donepezil hydrochloride. Aricept Evess is available in two strengths:
5mg white tablets marked 'ARICEPT' on one side and '5' on the other, containing 5mg of donepezil hydrochloride.
10mg yellow tablets marked 'ARICEPT' on one side and '10' on the other, containing 10mg of donepezil hydrochloride. The tablets are supplied in packs of 28.
Other ingredients include: mannitol, silica colloidal anhydrous, k-carrageenan, polyvinyl alcohol.
Additionally, the 10mg tablet contains synthetic yellow iron oxide (E172).

Marketing Authorisation Holder and Manufacturer

The Marketing Authorisation Holder is: Eisai Ltd., Hammersmith International Centre, 3 Shortlands, London W6 8EE, UK.
Aricept Evess tablets are manufactured for Eisai Ltd. by:
Pfizer PGM, 29, Route des Industries, 37530 Poce-sur-Cisse, France.

What is ARICEPT Evess and what is it for?

Aricept Evess (donepezil hydrochloride) belongs to a group of medicines called acetylcholinesterase inhibitors. It is used to treat the symptoms of dementia in people diagnosed as having mild to moderately severe Alzheimer's Disease. It is for use only in adult patients.

UNITED KINGDOM

Before using ARICEPT Evess tablets

You must not take Aricept Evess if:
- you are allergic to donepezil hydrochloride, or to piperidine derivatives, or to any of the ingredients used in the formulation as listed above
- you are pregnant, think you might be pregnant or are breast feeding

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 or other long term lung disease
- you have ever had any liver problems or hepatitis
- you have difficulty passing urine

Tell your doctor or pharmacist if you are taking any other medicines especially: pain killers or treatment for arthritis, antibiotics or anti-fungal medicine, muscle relaxants, anti depressants, anticonvulsants or medication for a heart condition.
If you are going to have an operation that requires you to have a general anaesthetic you should tell your doctor and the anaesthetist that you are taking Aricept Evess.
If you are in doubt, consult your doctor or pharmacist before using Aricept Evess tablets.
Tell your doctor or pharmacist the name of your caregiver. Your caregiver will help you to take your medicine as it is prescribed.
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 so. Also, your medicine can cause fatigue, dizziness and muscle cramp and if affected you must not drive or operate machinery.

YOU WILL FIND OUT MORE ABOUT ARICEPT EVESS ON THE BACK OF THIS LEAFLET

MORE INFORMATION ON ARICEPT EVESS

How to use ARICEPT Evess tablets

How much Aricept Evess should you take?
Take your Aricept Evess by mouth at night before you go to bed. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to your preference.
The tablet strength you will take may change depending on the length of time you have been taking the medicine and on what your doctor will recommend. Usually, you will start by taking 5mg (one white tablet) every night. After one month, your doctor may tell you to take 10mg (one yellow tablet) every night. The maximum recommended dose is 10mg 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. Do not stop taking the tablets unless told to do so by your doctor.
For how long should you take Aricept Evess?
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.
What if you take too many tablets?
DO NOT take more than one tablet each day. Call your doctor immediately if you take more than you should. If you cannot contact your doctor contact the local hospital Accident and Emergency department at once.
Always take the tablets and the carton with you to the hospital so that the doctor knows what has been taken.
What if you miss taking your tablets?
If you forget to take a tablet, just take one tablet the following day at the usual time. If you forget to take your medicine for more than one week, call your doctor before taking any more medicine.

After using ARICEPT Evess tablets

What side effects could Aricept Evess cause?
Like all medicines, Aricept Evess can have side effects. The most commonly reported side effects of Aricept Evess are diarrhoea, nausea, vomiting, muscle cramp, fatigue, and insomnia (difficulty in sleeping). Dizziness, headaches, pain, accidents and the common cold have also been reported.
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 Aricept Evess have also reported loss of appetite; hallucinations, agitation, aggressive behaviour; fainting, seizures; shaking, stiffness or uncontrollable movement especially of the face and tongue but also of the limbs; slow heart beat; abdominal disturbances including bleeding, stomach and duodenal ulcers; liver disorders including hepatitis; itching, rash and urinary incontinence.
You should tell your doctor if you have any of these or any other adverse effects while you are taking Aricept Evess.

How to look after your medicine (ARICEPT Evess tablets)

Do not store this medicine above 30°C. As with all medicines, the tablets should be kept in a safe place where children cannot see or reach them.
DO NOT use Aricept Evess after the expiry date that is printed on the label.
If your doctor tells you to stop taking your medicine, you should return any you have not used to your pharmacist.
This medicine is for you. Do not share it with anyone else even if they have the same symptoms as you.

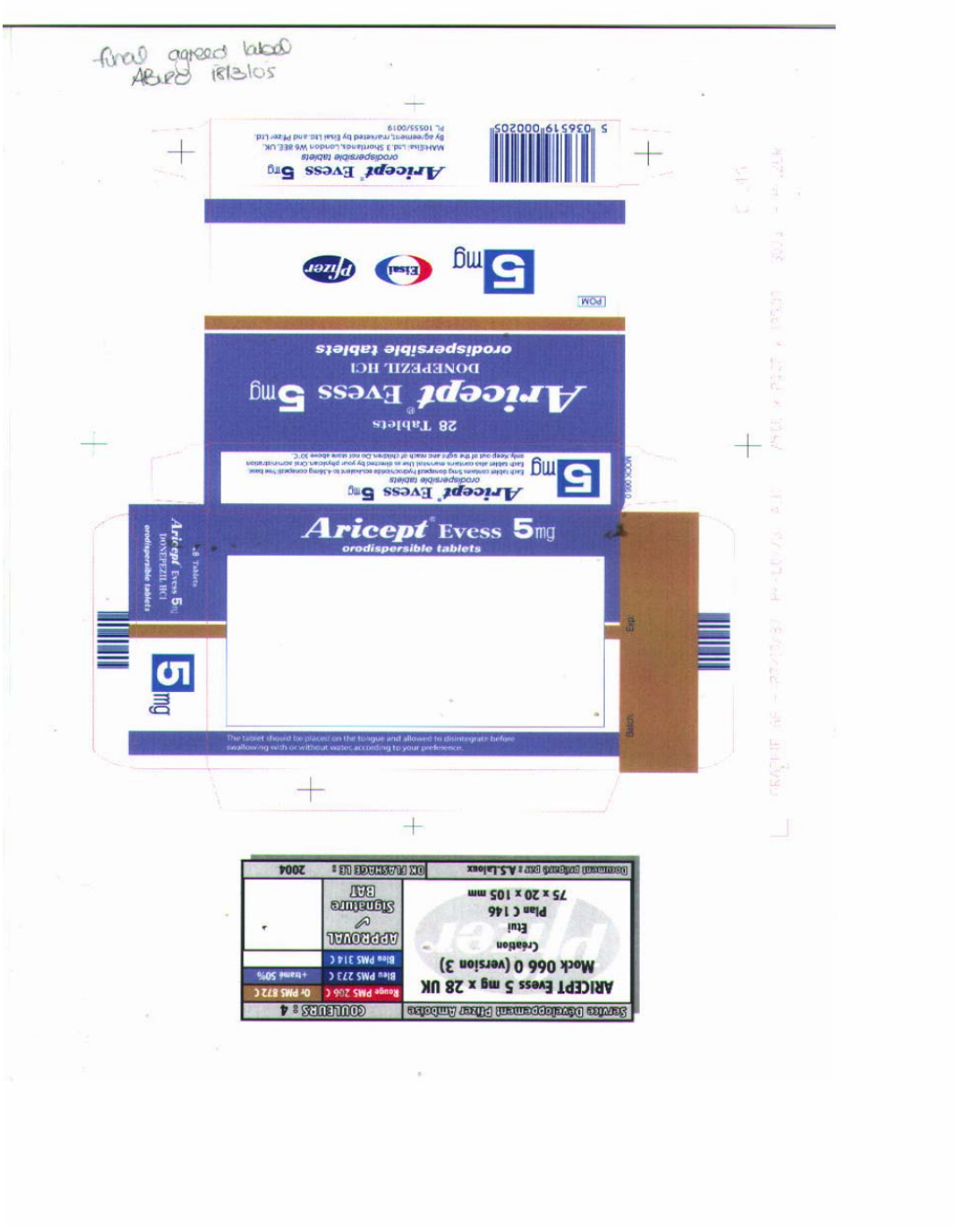
More information

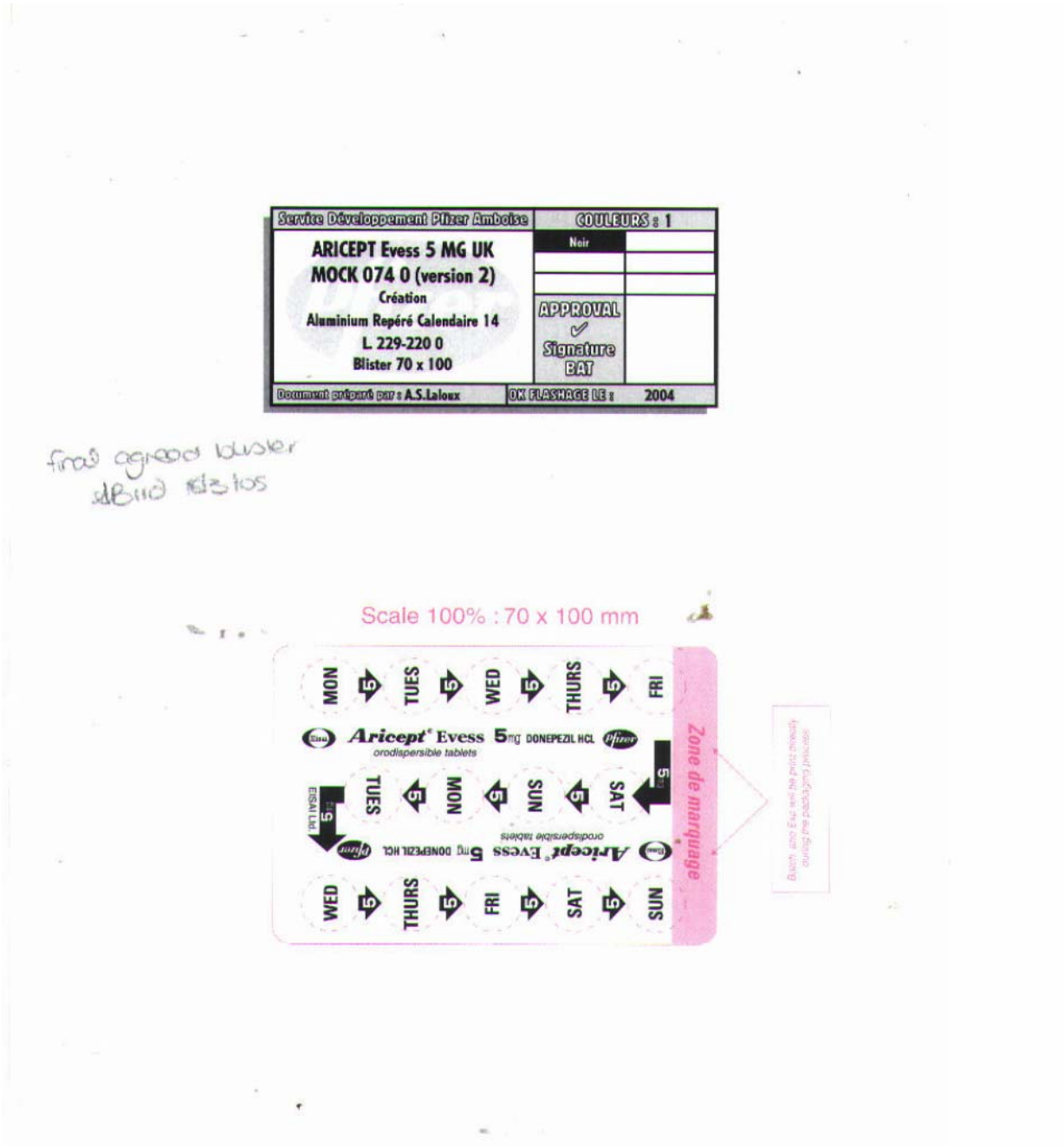
If you want to know more about your medicine, ask your doctor or pharmacist who can give you more information.
Date Aricept Evess Leaflet United Kingdom written December 2003

MOCK080 0

Module 4

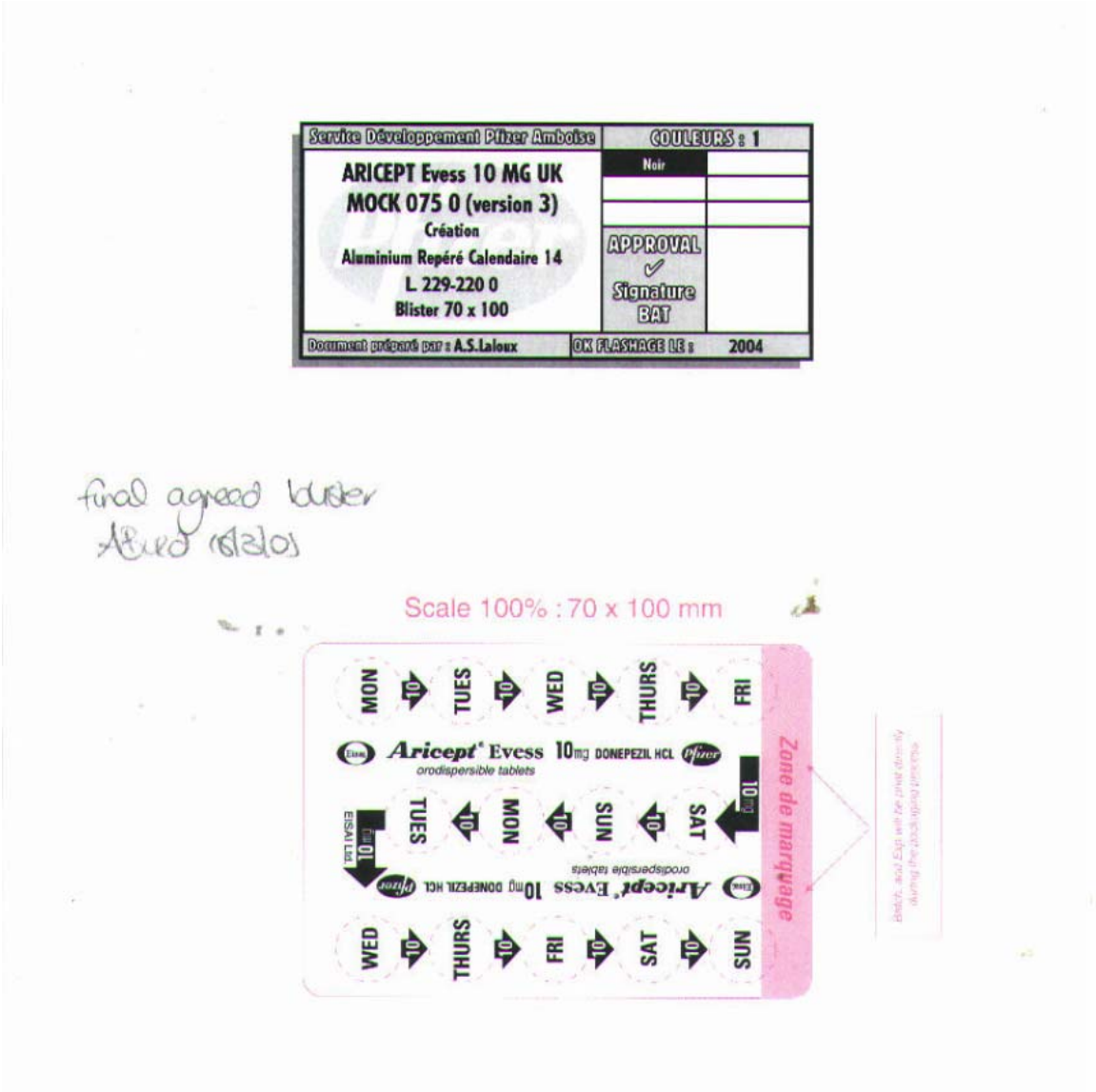
Labelling (5 mg Label)

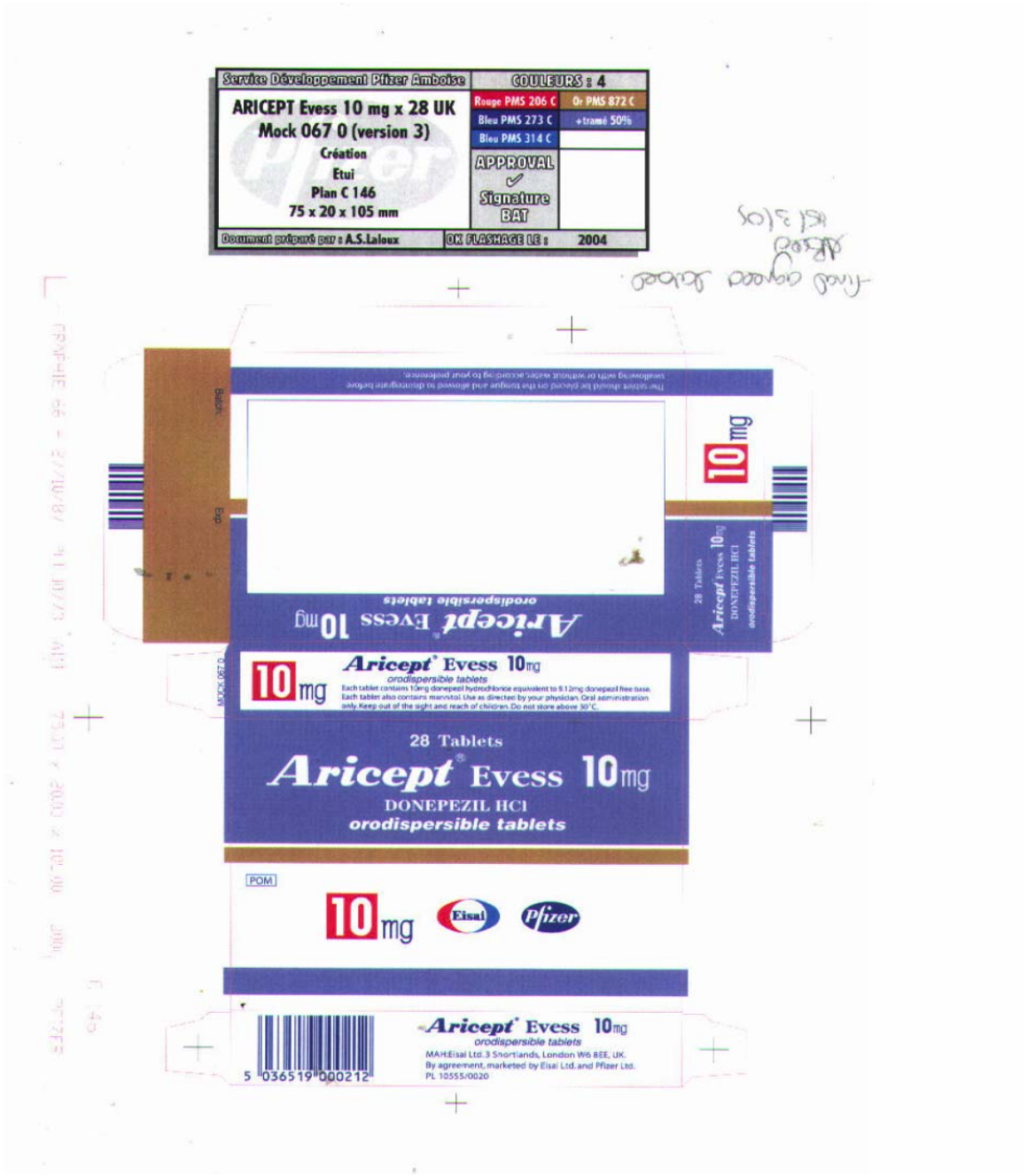



Service Développement Pfizer Amboise
COULEURS : 1
ARICEPT Evess 5 MG UK
MOCK 074 0 (version 2)
Création
Aluminium Repéré Calendaire 14
L 229-220 0
Blister 70 x 100
Noir
APPROVAL
Signature BAT
Document préparé par : A.S.Laloux
OK FLASHAGE LE : 2004
final agreed blister
Scale 100% : 70 x 100 mm
MON TUES WED THURS FRI
Aricept Evess 5mg DONEPEZIL HCL
orodispersible tablets
SAT SUN MON TUES
WED THURS FRI SAT SUN
Zone de marquage

(5mg Blister)

(10mg Blister)




Service Développement Pfizer Amboise
COULEURS : 4
ARICEPT Evess 10 mg x 28 UK
Mock 067 0 (version 3)
Création
Etui
Plan C 146
75 x 20 x 105 mm
Rouge PMS 206 C
Or PMS 872 C
Bleu PMS 273 C
+tramé 50%
Bleu PMS 314 C
APPROVAL
Signature
BAT
Document préparé par : A.S.Laloux
OK FLASHAGE LE :
2004
Batch
Exp.
10 mg
Aricept Evess 10mg
orodispersible tablets
28 Tablets
DONEPEZIL HCl
MOCK 067 0
Aricept Evess 10mg
orodispersible tablets
Each tablet contains 10mg donepezil hydrochloride equivalent to 8.12mg donepezil free base.
Each tablet also contains mannitol. Use as directed by your physician. Oral administration
only. Keep out of the sight and reach of children. Do not store above 30°C.
28 Tablets
Aricept Evess 10mg
DONEPEZIL HCl
orodispersible tablets
POM
10 mg
Eisai
Pfizer
5 036519 000212
Aricept Evess 10mg
orodispersible tablets
MAH:Eisai Ltd. 3 Shortlands, London W6 8EE, UK.
By agreement, marketed by Eisai Ltd. and Pfizer Ltd.
PL 10555/0020

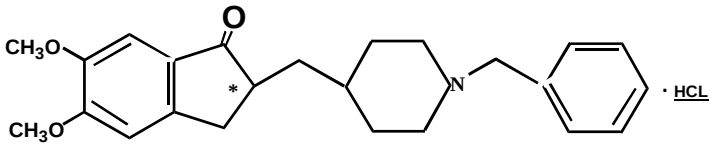
(10mg Label)

Module 5
Scientific discussion during initial procedure

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK considered that the application for Aricept Evess 5 and 10mg Tablets in the treatment of mild to moderately severe Alzheimer's dementia, could be approved. A national marketing authorisation was granted on the 17th May 2005.
These mutual recognition applications concern line extensions to Eisai's existing marketing authorisations for Aricept 5mg and 10mg film-coated tablets (PL 10555/0006-07), containing donepezil hydrochloride.

With the UK as reference member state in this mutual recognition procedure (MRP), the marketing authorisation holder (Eisai Limited) applied for marketing authorisations in Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Portugal, Sweden.
Aricept® Evess Tablets contain 5 mg or 10 mg donepezil hydrochloride, a piperidine based, reversible acetylcholinesterase inhibitor: (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidinyl]methyl]-1*H*-inden-1-one, hydrochloride (USAN and CAS).
The structural formula of donepezil HC1 is:



Donepezil HC1 has a molecular formula of $C_{24}H_{29}NO_3$·HC1 and a molecular weight of 415.96. It is commonly referred to in the pharmacological literature as E2020.

The UK was 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 within the community, the UK has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the UK 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.

PHARMACEUTICAL ASSESSMENT

Drug substance

Donepezil hydrochloride, the active substance, is manufactured by Eisai Company Limited, and Pfizer Inc. Donepezil hydrochloride is not subject to a Ph Eur or BP monograph, hence a full dossier has been provided for these applications.

The synthetic route for the manufacture of the active is identical to that used for the manufacture of active used in Aricept 5mg and 10mg tablets, which have already been granted a national licence in the UK and undergone an MRP. A brief overview of the synthetic route is provided rather then a full assessment of the data. The only variation submitted since granting the national licenses for Aricept 5mg and 10mg tablets has been to change the nature of the solvents.

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

An appropriate specification is provided for donepezil hydrochloride. The tests carried out on the drug substance include physical appearance, identification, assay, related substances and residual solvents.

Drug product

The objective of the development programme was to develop a globally acceptable, stable, orodispersible form of donepezil hydrochloride. The orodispersible forms were tested against Aricept 5 and 10mg Tablets for dissolution and found to be sufficiently comparable. The manufacturing procedure has been successfully validated. All excipients are European Pharmacopoeial grade, or USP grade. The bulk packaging (for transporting to the blister packaging site) is an aluminium foil pouch. The immediate packaging is 5-ply blisters, composed of PVC/PVdC/PE. The packaging materials comply with the European Pharmacopoeia. Neither the active substance nor excipients contain materials of animal origin.

A bioequivalence study has been performed on the orodispersible form of donepezil hydrochloride versus Aricept Tablets. Parameters such as area under the curve, zero to infinity, observed maximum plasma drug concentration and time to maximum plasma drug concentration were addressed. Based on these data it can be considered that the orodispersible form and the reference product are equivalent.

The proposed finished product specifications are in compliance with the general pharmacopoeial requirements and the batch data submitted, and are controlled with valid methods. The tests used in the finished product specification include appearance,

identification, water content, impurities, dissolution, disintegration, content uniformity, assay and microbiological tests.

Stability studies have been undertaken with stability data results supporting a shelf life of 36 months for bulk packed tablets and 24 months for blister packaged tablets. Stability studies were undertaken according to ICH guidelines.

Description and composition of the drug product

A description of both of the tablets is provided. In the case of the 5mg tablet, it is a white tablet with "Aricept" on one side and "5" on the other. In the case of the 10mg tablet, it is a yellow tablet, with "Aricept" on one side and "10" on the other. It is noted that a common granule is used in the manufacture of both tablet strengths.

			Unit Formula (mg/tablet)	
Name of Ingredient	**Function**	**Specification**	**5mg**	**10mg**
Donepezil hydrochloride	Active	Eisai standard	5	10
Mannitol				
Silica, colloidal anhydrous				
κ-Carrageenan				
Polyvinyl alcohol				
Ferric oxide (yellow)				

Tablets are packed into 5-ply blister strips, with 14 tablets per strip and then packed into cartons with 28 tablets per carton.

Pharmaceutical Development

Components of the drug product

Drug substance

Donepezil hydrochloride is a white to off-white solid. Identification is achieved by IR spectroscopy. The particle size was chosen in support of the demonstration of pharmaceutical and bioequivalence to the currently licensed product and as such is considered satisfactory.

Excipients

The excipients used for the orodispersible tablet formulation have been provided and are mannitol, silica, colloidal anhydrous, k-Carrageenan, purified water, polyvinyl alcohol, yellow ferric oxide (10mg only) and ethanol.

The choice and quantity of excipients developed for this product are adequately supported by data provided during the product's development.

Drug Product

Formulation Development

The orodispersible dosage form was chosen for this product in view of the target patient population. The tablet strengths are distinguishable by a colour change and embossing, with the 5mg presented as a white tablet with a "5" embossed on one side and the 10mg tablet presented as a yellow tablet with a "10" embossed on one side. Both tablet strengths have "Aricept" embossed on the other side. Data is provided for the formulation of the product used in the clinical trial studies for the tablets. It is noted that the formulations for the products in Japan are different to the ones proposed for the EU and US, with different strengths (3mg and 5mg) and smaller tablet size in the Japanese product. A bioequivalence study was also carried out to support this application for a line extension and this will be commented on later (see Section V – Bioequivalence).

A comparison of the dissolution profiles of the proposed product compared to the commercially available Aricept film-coated tablet was performed.

Manufacturing Process Development

A non-standard tabletting technology is employed in the manufacture of this drug product and a number of processing parameters were evaluated during the optimisation of the orodispersible tablets formulation.

Manufacture

A flow diagram is provided for the manufacturing process. Adequately detailed descriptions of the process are provided for the sites involved.

Batch Formula

Appropriate data have been provided on batches, for both strengths, manufactured at a production scale in the designated facility. These demonstrate compliance with the proposed specifications for the 5 and 10mg presentations.

Description of Manufacturing Process & Process Controls

Details are provided as both a narrative and a flow chart of the manufacturing process including the in-process controls.

Controls of Critical Steps & Intermediates

In process controls are set and a rationale is provided for the controls proposed at various stages in the process.

Process validation & evaluation

Process validation was carried out on full-scale batches made at the proposed manufacturing site. The data provided confirm that the process is well controlled and reproducible for both tablet strengths.

Control of excipients

All excipients are adequately controlled before use during the manufacturing process.

Justification of Specifications
No justification was deemed necessary for those excipients that are controlled by the Ph.Eur and the US national formulary. The necessary tests required confirming the quality of the material is deemed to be covered by the specification provided.

Excipients of Human or Animal Origin
A BSE/TSE risk status certificate is included for mannitol stating that it manufactured without any raw materials of animal origin.

Control of Drug Product

Specifications

Suitable tests and limits are proposed for the control of preparations of the 5mg and 10mg presentations.

Analytical Procedures & Validation of Analytical Procedures

Analytical methods have been successfully validated in accordance to ICH guidelines or are pharmacopoeial methods. A comprehensive validation package has been submitted for all the analytical methods.

Batch Analyses
Appropriate batch analytical data has been provided on batches of product manufactured at a production scale in the designated facility. These demonstrate compliance with the proposed release specification.

Justification of Specification(s)
The release specification for both strengths of orodispersible tablets has been adequately justified in the application.

Reference Standards of Materials
A primary working standard is specified for donepezil hydrochloride.

Container Closure System
The bulk packaging is an aluminium foil pouch into which the tablets are bulk packed for transport to the blister packaging site.

Stability
The stability data presented demonstrated that the drug is stable in the proposed formulation under real-time and accelerated storage. The data provided are supportive of the 24 month shelf life with no additional storage precautions required. Stability studies have been undertaken according to ICH guidelines.

Stress testing and photostability testing have also been carried out.
The applicant has also provided the results of transportation tests performed which assessed the potential for damage to the finished product during transportation to the packaging site. All results provided demonstrate that the proposed packaging type is suitable for transport of the bulk product to the packaging site.

Bioequivalence Studies
A full bioequivalence study is reported. The study was a single dose, randomised, balanced, two-period, two-treatment, crossover study in healthy volunteers with the following products using either a single dose of 5 or 10mg tablets:
Test (A): Either 5mg or 10mg donepezil hydrochloride rapid-dissolution tablets manufactured at Eisai, Japan
Reference (B): Either Aricept 5mg or 10mg tablets manufactured at Pfizer, France
The test product produced with the named active source was manufactured to the proposed formula. The manufacturing batch size for number of tablets was a satisfactory size for use as a biobatch. Certificates of analysis were provided for both batches of the test compound and were satisfactory.
Results from the bioequivalence study, comparing the orodispersible form (Aricept Evess 5 and 10mg Tablets) with the reference product (Aricept 5 and 10mg Tablets), showed bioequivalence between the two forms (according to the CPMP criteria).

A summary of product characteristics was provided for each of the tablet strengths. The SPCs are in line with the current SPC for the licensed product.

Labelling and Leaflets
Full colour mock-ups of the cartons are provided for both tablet strengths and for all pack sizes. Line drawings are also provided of the blister packs for both tablet strengths and all labelling is satisfactory.
The leaflet is considered satisfactory.

Information about the expert
A pharmacist with experience in the pharmaceutical industry wrote the pharmaceutical quality overall summary.
The report is a critical overview of the data submitted for the drug substance and product and was generally well written. The report is dated June 2005.

CLINICAL ASSESSMENT

INTRODUCTION AND BACKGROUND

These are full applications under Article 8.3(i) of EC Directive 2001/83, for line extensions to the applicant's products Aricept 5mg and 10mg, PL 10555/0006 and 7. The change is a new pharmaceutical form, orodispersible tablets.

The original film-coated tablet products were licensed in the UK on 14 February 1997 and were subsequently licensed in the EU via MR procedures with the UK as the RMS.

This proposed product has not been authorised in any other EU member state, nor is it the subject of any pending application in any other EU member state. National Scientific Advice was provided by the MHRA on 17 September 2003.

Donepezil is well characterised in the literature. It is a specific and reversible inhibitor of acetylcholinesterase, the predominant cholinesterase in the brain.

INDICATIONS

The applicant submitted the following proposed indication:

> Aricept Evess tablets are indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia

This is essentially identical to the SPC text approved for the film-coated tablet products.

DOSE & DOSE SCHEDULE

The applicant has submitted the following proposed text of section 4.2 of the SPC:

Adults/Elderly:
Treatment is initiated at 5 mg/day (once-a-day dosing). Aricept Evess should be taken orally, in the evening, just prior to retiring. The tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water, according to patient preference. 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 Aricept Evess 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.

Upon discontinuation of treatment, a gradual abatement of the beneficial effects of Aricept is seen. There is no evidence of a rebound effect after abrupt discontinuation of therapy.

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:
Aricept is not recommended for use in children.

No new preclinical data have been supplied with these applications and none are required, however, a preclinical expert report, summarising relevant non-clinical studies, has been included in the MR dossier; this is satisfactory.

The pharmacodynamics and kinetics of donepezil are well described. No new PK or PD data are submitted. A single bioequivalence study was presented, comparing Aricept Evess 5mg and 10mg with the reference Aricept tablets, 5mg and 10mg, marketed in the UK. It was carried out in compliance with Good Clinical Practice by a CRO in 2001.

Bioequivalence study

In this comparative, randomised, two-way, two-period, single-dose crossover study, in healthy fasted male and female volunteers, on two occasions the subjects received either the applicant's test product Aricept Evess or the reference product Aricept tablets. Half of the subjects received the 5mg strength of both test and reference products whilst the other half received 10mg.

Serum drug levels were followed in accordance to the study protocol and a washout period between phases was also carried out in accordance with the study protocol.

Data for AUC_t, AUC_{inf} and C_{max} were analysed by ANOVA, both log-transformed and non-transformed. T_{max} was analysed non-parametrically.

Results

Data analysed from the bioequivalence study, comparing the orodispersible form (Aricept Evess 5 and 10mg Tablets) with the reference product (Aricept 5 and 10mg Tablets) showed bioequivalence between the two products (according to the CPMP criteria).

Bioequivalence results for log-transformed data with 90% Confidence Intervals:

5mg dose

AUC_t	1.05 (1.02 – 1.08)
AUC_{inf}	1.05 (1.01 – 1.09)
C_{max}	0.98 (0.92 – 1.04)

10mg dose

AUC_t	1.03 (0.99 – 1.07)
AUC_{inf}	1.03 (0.99 – 1.08)
C_{max}	0.97 (0.92 – 1.02)

The individual patient data are generally reassuring, showing mostly good superimposability of the plots and indicating the slow elimination of donepezil (plasma half life approximately 3 days).

Bioequivalence for both strengths was satisfactorily demonstrated in accordance with CPMP criteria.

EFFICACY

No new data have been submitted with these applications and none are required.

SAFETY

No new data have been submitted with these applications and none are required. There were no important adverse events in the bioequivalence study and the literature review in the expert report identifies no new safety issues.

EXPERT REPORTS

A satisfactory expert report is provided by, an appropriately qualified individual employed by the applicant. It includes a summary of the bioequivalence study and an up-to-date, well-referenced review of the published literature relating to the pharmacology, efficacy and safety of donepezil.

PATIENT INFORMATION LEAFLET (PIL)

The PIL text is mostly identical to that approved for the film-coated tablet products, except for advice on how to take the orodispersible tablets. A full colour mock-up has been supplied.

LABELLING

The labelling is satisfactory. Full colour mock-ups are supplied.

APPLICATION FORM (MAA)

The MAA is medically satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS

The SPC is mostly identical to that approved for the film-coated tablet products, except for advice that the tablet should be placed on the tongue and allowed to disintegrate before swallowing with or without water.

DISCUSSION

The requested indications and other SPC details are satisfactory and bioequivalence to the film-coated tablet products has been shown.

The SPC is satisfactory. The rest of the product literature including PIL and labelling are satisfactory.

MEDICAL CONCLUSION

Marketing authorisations may be granted for these products.