

**ARICEPT 1MG/ML ORAL SOLUTION
PL 10555/0018**

UKPAR

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**ARICEPT LIQUID 1MG/ML ORAL SOLUTION
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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Eisai Limited a Marketing Authorisation (licence) for the medicinal product Aricept 1mg/ml Oral Solution (PL 10555/0018) on 31st October 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 this application and it was therefore judged that the benefits of taking Aricept 1mg/ml Oral Solution outweigh the risks; hence a Marketing Authorisation has been granted.

**ARICEPT LIQUID 1MG/ML ORAL SOLUTION
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SCIENTIFIC DISCUSSION

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INTRODUCTION

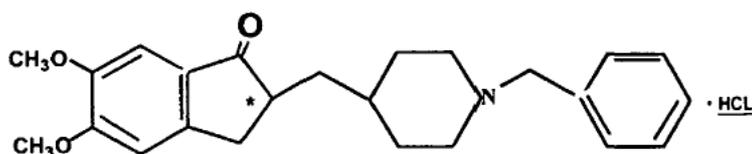
Based on the review of the data on quality, safety and efficacy, the MHRA granted Eisai Limited a Marketing Authorisation for the medicinal product Aricept Liquid 1mg/ml Oral Solution (PL 10555/0018) on 31st October 2008. This is a prescription-only medicine used to treat the symptoms of dementia in people diagnosed as having mild to moderately severe Alzheimer's disease. The symptoms include increasing memory loss, confusion and behavioural changes.

This national abridged standard application is for Aricept Liquid 1mg/ml oral solution and is made under EC Article 8.3 (i); a complete application for a known active substance. The application for an oral solution is made as a line extension to Eisai's existing marketing authorisations for Aricept 5mg and 10mg film-coated tablets (PL 10555/0006-07, granted February 1997). As a result no new clinical or preclinical studies, apart from the bioequivalence study have been submitted with the application.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Donepezil hydrochloride

Nomenclature:**INN:** Donepezil hydrochloride**Chemical name:** (±)-2,3-dihydro-5,6-dimethoxy-2-[[1-(phenylmethyl)-4-piperidiny]methyl]-1H-inden-1-one, hydrochloride**Structure:****Molecular formula:** C₂₄H₂₉N₀₃. HCl**Molecular weight:** 415.96**Physical form:**

Donepezil HCl is a white crystalline powder,

Solubility:

Freely soluble in chloroform, soluble in water and in glacial acetic acid, slightly soluble in ethanol and in acetonitrile, and practically insoluble in ethyl acetate and in n-hexane.

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.

DRUG PRODUCT**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely D-Dorbitol solution 70%, povidone K30, citric acid anhydrous, sodium citrate, sodium benzoate, methyl parahydroxybenzoate, propylene glycol, sodium metabisulphite, purified water, strawberry flavour 50109A. Appropriate justification for the inclusion of each excipient has been provided.

The excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients. There were no novel excipients used.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory. The formulation was developed with the target group in mind in that a liquid formulation was would enable better compliance than the currently available film coated tablet.

Characterisation of Impurities

The potential impurities in the solution have been named and limits applied. Sufficient data for a forced degradation study carried out on the finished product. Chromatograms for each of the named impurities prepared at or near both the limits of detection and quantitation have been provided.

Manufacture

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

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

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any standards used.

Container Closure System

Packaging consists of a 300mL white high density polyethylene (HDPE) bottle and a polypropylene child resistant cap. A 10 ml polypropylene CE marked measuring cup, graduated at 5 ml and 10 ml, is also provided.

Specifications and Certificates of Analysis for the packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC, regarding contact with food. The product is packaged in a pack size of 300mL.

Stability

Stability data were generated on six production scale batches of product manufactured at the intended site and stored in the intended packaging.

The data presented demonstrate that the drug is stable in the proposed formulation under both real-time and accelerated storage. Little or no changes are noted in the results and no stability trends are observable in the data. An in-use stability test was also performed over the proposed shelf life of 60 days once opened. The results show that there is no trend towards degradation of the product under normal in-use conditions. Based on the results, a shelf life of 24 months is made for the unopened bottle and for 60 days once opened which is satisfactory. Storage conditions are “Keep bottle in the outer container”. No special temperature storage conditions are required for this product.

Patient Information Leaflet

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL 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 grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

1. BACKGROUND

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

2. INDICATIONS

The applicant has submitted the following:

Aricept Liquid is indicated for the symptomatic treatment of mild to moderately severe Alzheimer's dementia.

The above is essentially identical to the SPC text approved for the film coated tablets.

3. 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 ml (5 mg)/day (once-a-day dosing) by filling the dosing cup to the lower line. Aricept Liquid should be taken orally, in the evening, just prior to retiring, and can be taken with or without food.

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 Liquid can be increased to 10 ml (10 mg)/day (once-a-day dosing), by filling the dosing cup to the upper line. 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 Liquid 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.

The proposed text is essentially identical to the SPC text approved for the film coated tablet products.

4. TOXICOLOGY

A pre-clinical assessment report is provided.

5. CLINICAL PHARMACOLOGY

The pharmacodynamics and kinetics of donepezil are well described. No new PD data are submitted. Two key new PK studies are presented. A further bioequivalence study (013) used the U.S. product as comparator and is therefore not of direct relevance in terms of bioequivalence for the purpose of this application.

The Aricept liquid formulation used in the new PK studies is identical to that proposed for marketing except that it contained a different strawberry flavour (PFC 9952). PFC 9952 has not been used in pharmaceuticals or food in the EU. Following scientific advice given by the MHRA to the company on 17 September 2003 the company reformulated the product to replace PFC9952 with a flavour used in the EU.

The company has provided satisfactory justification that the flavouring excipient would not be expected to influence bioavailability. The UK assessor therefore agrees that the validity of the bioequivalence study is unaffected and that a new bioequivalence study is not required for the reformulated product with the new flavouring.

The company proposes to provide a CE-marked dosing cup for administering the product. However the Aricept liquid was administered via a syringe in the bioequivalence studies. The clinical expert has discussed the implications of this (section 2.5.6.2). The UK assessor agrees that the validity of the bioequivalence study is unaffected and that the CE-marked dosing cup is a satisfactory method for administering the product.

STUDY E2020-E044-019

Study 019 was a bioequivalence study comparing Aricept liquid with the reference Aricept 5mg and 10mg tablets marketed in the UK. It was carried out in compliance with Good Clinical Practice by Hammersmith Medicines Research, a CRO in London in 2001.

In this comparative, randomised, two-way, two-period, single dose crossover study, 32 healthy fasted male and female volunteers were randomised to receive on two occasions either Aricept liquid or the reference product Aricept tablets (marketed in the EU, including the UK).

Serum drug levels were followed for 10 days following dosing. Sampling was sufficient to ensure accurate estimation of AUC_{inf}.

As the elimination half life is approximately 3 days the washout period between phases was 3 weeks. There was apparently no carryover into the second period as baseline (pre-dosing) values for donepezil concentrations were reported as 0.000ng/ml (i.e. below the limit of assay detection) for all subject for both periods.

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

Results

5 subjects discontinued the study and were excluded from the analysis. Another subject who missed 2 visits in each period was also excluded from the analysis. These exclusions were according to protocol and the conclusions of the study are not considered to be significantly affected.

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

AUC_t	0.939 (0.905 – 1.081)
AUC_{inf}	0.948 (0.912 – 0.985)
C_{max}	0.960 (0.908 – 0.975)
T_{max}	2.0 hrs test, 2.0 hrs reference

The individual patient data are generally reassuring, showing mostly good superimposability of the plots and indicating the slow elimination of donepezil (plasma half life 66 – 69 hours).

Assessor's Comment

Bioequivalence to the licensed tablet formulation has been satisfactorily demonstrated in accordance with CPMP criteria. The 90% Confidence Intervals do not include unity and the numbers therefore suggest that the liquid might have slightly lower bioavailability than the tablet. It would be unusual for an oral solution to have lower bioavailability than the corresponding tablet. It seems likely to be a statistical quirk; the 95% Confidence Intervals (and certainly the 99% CIs) would probably include unity. This is largely irrelevant as the 90% Confidence Intervals all fall well within the 80-125% standard criteria.

STUDY E2020-E044-018

Study 018 was a food effect study examining the effect of food on the absorption of Aricept liquid. It was carried out in compliance with Good Clinical Practice at the PRACS institute, Fargo, USA. The study is not a regulatory requirement for this application as it is only necessary to show bioequivalence of Aricept liquid to the reference Aricept 5mg and 10mg tablets in the fasting state.

It was a comparative, randomised, two-way, two-period, single dose crossover study of standard design. 20 healthy fasted male and female volunteers were randomised to receive Aricept liquid on two occasions, either fasted or after a high fat meal. The washout period between phases was at least 2 weeks.

Bioequivalence results for fed/fasted with 90% Confidence Intervals:

AUC₀₋₇₂ hrs	0.94 (0.87 – 1.00)
C_{max}	0.83 (0.74 – 0.92)
T_{max}	4.0 hrs fed, 3.1 hrs fasted

Assessor's Comment

Bioavailability may be slightly reduced in the fed state but not by a clinically important amount. The rate of absorption is moderately reduced. The SPC states that the product “can be taken with or without food” (section 4.2). Section 5.2 provides the following information:

Administration of Aricept Liquid with food reduces the rate but not the extent of donepezil absorption. Co-administration of a high-fat meal with a single 10mg dose reduced the C_{max} by 17% and delayed the T_{max} by approximately 1 hour, but had no effect on AUC₀₋₇₂. Drug administration with food therefore has no influence on average steady-state plasma concentrations.

This is satisfactory.

6. EFFICACY

No new data submitted and none required.

7. SAFETY

No new data submitted.

8. EXPERT REPORTS

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

9. PATIENT INFORMATION LEAFLET (PIL)

The PIL text is mostly identical to that approved for the film coated tablet products, except for advice specific to the liquid formulation; in particular dosing and warnings relating to the excipients. The PIL text is satisfactory. A full colour mock-up should be supplied.

10. LABELLING

The labelling monochrome mock-ups are satisfactory. Full colour mock-ups should be supplied.

11. APPLICATION FORM (MAA)

The MAA is medically satisfactory.

12. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is mostly identical to that approved for the film coated tablet products, except for the administration advice appropriate for the liquid formulation, additional warnings and contraindications relating to the different excipients, and PK information on the liquid formulation. The changes are all formulation specific and are satisfactory.

13. DISCUSSION

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

The SPC is mostly identical to the SPC for the film coated tablet product approved in the UK. The changes are all formulation specific and are satisfactory. The rest of the product literature including PIL and labelling are satisfactory.

14. MEDICAL CONCLUSION

A marketing authorisation may be granted for this preparation.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Aricept Liquid Oral Solution 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 an application of this type.

EFFICACY

No new data on clinical efficacy or safety were presented for this application and none were required.

No new unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The SPC, PIL and labelling are satisfactory and consistent with that of the original products Aricept 5mg and 10mg Film Coated Tablets (PL 10555/0006-7).

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.

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 data provided in support of this application are acceptable. The risk: benefit is, therefore, considered to be positive.

**ARICEPT LIQUID 1MG/ML ORAL SOLUTION
PL 10555/0018**

STEPS TAKEN FOR ASSESMENT

- 1 The MHRA received the marketing authorisation application on 21st May 2004.
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 25th June 2004.
- 3 Following assessment of the application the MHRA requested further information relating to the quality dossier on 6th December 2005 and 22nd February 2007.
- 4 The applicant responded to the MHRA's request, providing further information for the quality sections of the dossier on 11th November 2006 and 9th June 2008.
- 5 The application was determined on 31st October 2008.

**ARICEPT LIQUID 1MG/ML ORAL SOLUTION
PL 10555/0018**

STEPS TAKEN AFTER AUTHORISATION-SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Aricept Liquid 1mg/ml Oral Solution is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Aricept Liquid 1 mg/ml oral solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

5 mg/5ml of donepezil hydrochloride, equivalent to 4.56 mg/5ml donepezil free base.

D-Sorbitol (E420) 1785 mg /5ml

Sodium benzoate (E211) 5 mg /5ml

Methyl parahydroxybenzoate (E218) 5 mg /5ml

Sodium metabisulphite (E223) 1 mg /5ml.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

oral solution.

A clear, colourless to light yellow liquid with a strawberry odour that is essentially free from visible foreign matter.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Aricept Liquid 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 ml (5 mg)/day (once-a-day dosing) by filling the dosing cup to the lower line. Aricept Liquid should be taken orally, in the evening, just prior to retiring, and can be taken with or without food.

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 Liquid can be increased to 10 ml (10 mg)/day (once-a-day dosing), by filling the dosing cup to the upper line. 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 Liquid 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 Liquid is contraindicated in patients with a known hypersensitivity to donepezil hydrochloride or piperidine derivatives.

Aricept Liquid is also contraindicated in patients with hereditary fructose intolerance and patients with hypersensitivity to metabisulphites or any other excipients used in the formulation (see also section 4.8 Undesirable effects).

4.4 Special warnings and precautions for use

The use of Aricept 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.

Sodium benzoate and methyl parahydroxybenzoate may cause skin & mucous membrane irritation, urticaria and contact dermatitis (see also section 4.8 Undesirable effects).

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 sinus pauses should be considered.

Gastrointestinal Conditions: Patients at increased risk for developing ulcers, e.g. those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored for symptoms. However, the clinical studies with 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.

Mortality in Vascular Dementia Clinical Trials

Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS-AIREN criteria for probable or possible vascular dementia (VaD). The NINDS-AIREN criteria are designed to identify patients whose dementia appears to be due solely to vascular causes and to exclude patients with Alzheimer's disease. In the first study, the mortality rates were 2/198 (1.0%) on donepezil hydrochloride 5 mg, 5/206 (2.4%) on donepezil hydrochloride 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on donepezil hydrochloride 5 mg, 3/215 (1.4%) on donepezil hydrochloride 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on donepezil hydrochloride 5 mg and 0/326 (0%) on placebo. The mortality rate for the three VaD studies combined in the donepezil hydrochloride group (1.7%) was numerically higher than in the placebo group (1.1%), however, this difference was not statistically significant. The majority of deaths in patients taking either donepezil hydrochloride or placebo appear to result from various vascular related causes, which could be expected in this elderly population with underlying vascular disease. An analysis of all serious non-fatal and fatal vascular events showed no difference in the rate of occurrence in the donepezil hydrochloride group relative to placebo.

In pooled Alzheimer's disease studies (n=4146), and when these Alzheimer's disease studies were pooled with other dementia studies including the vascular dementia studies (total n=6888), the mortality rate in the placebo groups numerically exceeded that in the donepezil hydrochloride groups.

4.5 Interaction with other medicinal products and other forms of interaction

Donepezil hydrochloride and/or any of its metabolites do not inhibit the metabolism of theophylline, warfarin, cimetidine or digoxin in humans. The metabolism of donepezil hydrochloride is not affected by concurrent administration of digoxin or cimetidine. In vitro studies have shown that the cytochrome P450 isoenzymes 3A4 and to a minor extent 2D6 are involved in the metabolism of donepezil. Drug interaction studies performed in vitro show that ketoconazole and quinidine, inhibitors of CYP3A4 and 2D6 respectively, inhibit donepezil metabolism. Therefore, these and other CYP3A4 inhibitors, such as itraconazole and erythromycin, and CYP2D6 inhibitors, such as fluoxetine, could inhibit the metabolism of donepezil. In a study in healthy volunteers, ketoconazole increased mean donepezil concentrations by about 30%. Enzyme inducers, such as rifampicin, phenytoin, carbamazepine and alcohol may reduce the levels of donepezil. Since the magnitude of an inhibiting or inducing effect is unknown, such drug combinations should be used with care. Donepezil hydrochloride has the potential to interfere with medications having anticholinergic activity. There is also the potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists or beta blocking agents 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 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 adverse events are diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.

Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: very common (> 1/10) common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1,000); very rare (< 1/10000) and not known (cannot be estimated from available data).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The pharmacotherapeutic group: anti-dementia drugs; anticholinesterase; ATC-code N06DA02.

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

Alzheimer's Dementia

In patients with Alzheimer's Dementia participating in clinical trials, administration of single daily doses of 5 mg or 10 mg of 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 cannot be considered to have any effect on the progress of the disease.

Efficacy of treatment 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%**
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*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.

Administration of Aricept Liquid with food reduces the rate but not the extent of donepezil absorption. Co-administration of a high-fat meal with a single 10mg dose reduced the C_{max} by 17% and delayed the T_{max} by approximately 1 hour, but had no effect on AUC₀₋₇₂. Drug administration with food therefore has no influence on average steady- state plasma concentrations.

Distribution: Donepezil hydrochloride is approximately 95% bound to human plasma proteins. The plasma protein binding of the active metabolite 6-O-desmethyldonepezil is not known. The distribution of donepezil hydrochloride in various body tissues has not been definitively studied. However, in a mass balance study conducted in healthy male volunteers, 240 hours after the administration of a single 5 mg dose of ¹⁴C-labelled donepezil hydrochloride, approximately 28% of the label remained unrecovered. This suggests that donepezil hydrochloride and/or its metabolites may persist in the body for more than 10 days.

Metabolism/Excretion: Donepezil hydrochloride is both excreted in the urine intact and metabolised by the cytochrome P450 system to multiple metabolites, not all of which have been identified. Following administration of a single 5 mg dose of ¹⁴C-labelled donepezil hydrochloride, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil hydrochloride (30%), 6-O-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

D-Sorbitol (E420)
Povidone K-30 (E1201)
Citric acid anhydrous (E330)
Sodium citrate (E331)
Sodium benzoate (E211)
Methyl parahydroxybenzoate (E218)
Propylene glycol (E1500)
Sodium metabisulphite (E223)
Strawberry flavour
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years.
After first opening: 60 days

6.4 Special precautions for storage

Keep bottle in the outer container.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and Contents of Container

300 ml HDPE bottle with HDPE and polypropylene child-resistant cap. A 10 ml polypropylene CE marked measuring cup, graduated at 5 ml and 10 ml, is also provided.

6.6 Special precautions for disposal

The dosing cup should be washed with water after use and left to air dry.

7 MARKETING AUTHORISATION HOLDER

Eisai Limited,
Hammersmith International Centre,
3, Shortlands,
London
W6 8EE

8 MARKETING AUTHORISATION NUMBER(S)

PL 10555/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31/10/2008

10 DATE OF REVISION OF THE TEXT

31/10/2008

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

ARICEPT® LIQUID 1 mg/ml Oral Solution (Donepezil Hydrochloride)

You and your caregiver should 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET:

1. What ARICEPT Liquid is and what it is used for
2. Before you take ARICEPT Liquid
3. How to take ARICEPT Liquid
4. Possible side effects
5. How to store ARICEPT Liquid
6. Further information

1. WHAT ARICEPT IS AND WHAT IT IS USED FOR

ARICEPT (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. The symptoms include increasing memory loss, confusion and behavioural changes. As a result, sufferers of Alzheimer's disease find it more and more difficult to carry out their normal daily activities. ARICEPT Liquid is for use in adult patients only.

2. BEFORE YOU TAKE ARICEPT LIQUID

Do NOT take ARICEPT LIQUID

- if you are allergic (hypersensitive) to donepezil hydrochloride, or to piperidine derivatives, or any of the other ingredients of ARICEPT Liquid listed in section 6
- if you are breast feeding

Take special care with ARICEPT LIQUID

Tell your doctor or pharmacist before starting to take ARICEPT Liquid if you have or have had:

- stomach or duodenal ulcers
- seizures (fits) or convulsions
- a heart condition (irregular or very slow heart beat)
- asthma or other long term lung disease
- liver problems or hepatitis
- difficulty passing urine or mild kidney disease
- inherited intolerance of a sugar known as fructose

Also tell your doctor if you are pregnant or think you might be pregnant.

Taking other medicines

Please tell your doctor or pharmacist if you are taking, or have recently taken, any other medicine. This includes medicines that your doctor has not prescribed for you but which you have bought yourself from a chemist/pharmacist. It also applies to medicines you may take sometime in the future if you continue to take ARICEPT Liquid.

This is because these medicines may weaken or strengthen the effects of ARICEPT Liquid.

Especially tell your doctor if you are taking any of the following types of medicines:

- other Alzheimer's disease medicines, e.g. galantamine
- pain killers or treatment for arthritis e.g. aspirin, non-steroidal anti-inflammatory (NSAID) drugs such as ibuprofen, or diclofenac sodium
- anticholinergics medicines, e.g. tolterodine
- antibiotics e.g. erythromycin, rifampicin

More information can be found on the back of the leaflet.

- anti-fungal medicine e.g. ketoconazole
- anti-depressants e.g. fluoxetine
- anticonvulsants e.g. phenytoin, carbamazepine
- medication for a heart condition e.g. quinidine, beta-blockers (propranolol and atenolol)
- muscle relaxants e.g. diazepam, succinylcholine
- general anaesthetic
- medicines obtained without a prescription e.g. herbal remedies

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 Liquid. This is because ARICEPT Liquid may affect the amount of anaesthetic needed.

ARICEPT Liquid can be used in patients with kidney disease or mild to moderate liver disease. Tell your doctor first if you have kidney or liver disease. Patients with severe liver disease should not take ARICEPT Liquid.

Tell your doctor or pharmacist the name of your caregiver. Your caregiver will help you to take your medicine as it is prescribed.

Taking ARICEPT LIQUID with food and drink

Food will not influence the effect of ARICEPT Liquid.

ARICEPT Liquid should not be taken with alcohol because alcohol may change its effect.

Pregnancy and breast-feeding

ARICEPT Liquid must not be used while breastfeeding.

If you are pregnant, or think you might be pregnant, ask your doctor for advice before taking any medicine.

Driving and using machines

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 tiredness, dizziness and muscle cramp. If you experience any of these effects you must not drive or operate machinery.

Important information about some of the ingredients of ARICEPT LIQUID

This medicine contains:

- sorbitol (E420) - if you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product. Sorbitol is a source of fructose. A 5 ml dose of ARICEPT Liquid supplies 1.8 g of sorbitol and a 10 ml dose of ARICEPT Liquid supplies 3.6 g of sorbitol.
- methyl parahydroxybenzoate (E218) which may cause allergic reactions e.g. rash. The reaction may be delayed.
- sodium metabisulphite (E223) which may rarely cause hypersensitivity reactions e.g. rashes or swelling, especially of the tongue and lips and wheezing or coughing (bronchospasm).

3. HOW TO TAKE ARICEPT LIQUID

How much ARICEPT LIQUID should you take?

Usually, you will start by taking 5 ml every night. After one month, your doctor may tell you to take 10 ml every night. To take a 5 ml dose pour the liquid into the dosing cup to the lower line. To take a 10 ml dose pour the liquid into the dosing cup to the upper line. The amount of ARICEPT Liquid you will take may change depending on the length of time you have been taking the medicine and what your doctor recommends. The maximum recommended dose is 10 ml each night. After taking your dose you should wash the dosing cup with water and leave to air dry. 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.

More information can be found on the back of the leaflet.

For how long should you take ARICEPT LIQUID ?

Your doctor or pharmacist will advise you on how long you should continue to take your medicine. You will need to see your doctor from time to time to review your treatment and assess your symptoms.

If you stop taking ARICEPT LIQUID

Do not stop taking ARICEPT LIQUID unless told to do so by your doctor. If you stop taking ARICEPT LIQUID the benefits of your treatment will gradually fade away.

If you take more ARICEPT LIQUID than you should

DO NOT take more medicine than your doctor has told you to. 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 bottle and the carton with you to the hospital so that the doctor knows what has been taken. Symptoms of overdosing include feeling and being sick, drooling, sweating, slow heart rate, low blood pressure (light-headedness or dizziness when standing), breathing problems, losing consciousness and seizures (fits) or convulsions.

If you forget to take ARICEPT LIQUID

If you forget to take your medicine, just take your normal dose of medicine 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.

4. POSSIBLE SIDE EFFECTS

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

The following side effects have been reported by people taking ARICEPT Liquid.

Tell your doctor if you have any of these effects while you are taking ARICEPT Liquid.

Serious side effects:

You must tell your doctor immediately if you notice these serious side effects mentioned. You may need urgent medical treatment.

- liver damage e.g. hepatitis. The symptoms of hepatitis are feeling or being sick, loss of appetite, feeling generally unwell, fever, itching, yellowing of the skin and eyes, and dark coloured urine (probably affecting fewer than 1 in 1,000)
- stomach or duodenal ulcers. The symptoms of ulcers are stomach pain and discomfort (indigestion) felt between the navel and the breast bone (probably affecting fewer than 1 in 100)
- bleeding in the stomach or intestines. This may cause you to pass black tar like stools or visible blood from the rectum (probably affecting fewer than 1 in 100)
- seizures (fits) or convulsion (probably affecting fewer than 1 in 100)

Very common side effects (probably affecting more than 1 in 10):

- diarrhoea
- feeling or being sick
- headaches

Common side effects (probably affecting up to 1 in 10):

- muscle cramp
- tiredness
- difficulty in sleeping (insomnia)
- the common cold
- loss of appetite
- hallucinations (seeing or hearing things that are not really there)
- agitation
- aggressive behaviour
- fainting
- dizziness
- stomach feeling uncomfortable
- rash

- itching
- passing urine uncontrollably
- pain
- accidents (patients may be more prone to falls and accidental injury)

Uncommon side effects (probably affecting fewer than 1 in 100):

- slow heart beat

Rare side effects (probably affecting fewer than 1 in 1,000):

- stiffness, shaking or uncontrollable movement especially of the face and tongue but also of the limbs

You should tell your doctor if you notice any other side effects not listed in this leaflet while you are taking ARICEPT Liquid.

5. HOW TO STORE ARICEPT LIQUID

Keep bottle in the outer carton. This medicinal product does not require any special temperature storage conditions. Keep out of the reach and sight of children.

Use within 60 days of first opening the bottle. You may find it helpful to write the date you first opened the bottle in the space provided on the bottle label.

DO NOT use ARICEPT Liquid after the expiry date that is printed on the label. The expiry date refers to the last day of that month.

If your doctor tells you to stop taking your medicine, you should return any you have not used to your pharmacist.

6. FURTHER INFORMATION

What does ARICEPT LIQUID contain ?

The active substance is donepezil hydrochloride.

- 5 ml of Aricept Liquid contains 5 mg of donepezil hydrochloride
- 10 ml of Aricept Liquid contains 10 mg of donepezil hydrochloride
- The other ingredients are D-sorbitol (E420), povidone (E1201), citric acid (E330), sodium citrate (E331), sodium benzoate (E211), methyl parahydroxybenzoate (E218), propylene glycol (E1500), sodium metabisulphite (E223) and strawberry flavour.

What does ARICEPT LIQUID look like ?

ARICEPT Liquid is a colourless to light yellow liquid with a strawberry smell.

What is in a pack of ARICEPT LIQUID ?

Aricept Liquid is available in one strength of 1 mg/ml and is supplied in bottles of 300 ml. The package also includes a dosing cup.

Marketing Authorisation Holder

The Marketing Authorisation Holder is: Eisai Ltd., Hammersmith International Centre, 3 Shortlands, London W6 8EE, UK.

Manufacturer responsible for batch release

Eisai Manufacturing Limited
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Manufactured for Eisai Ltd. by: DSM Pharmaceuticals Inc., 5900 NW Greenville Boulevard, Greenville, N. Carolina 27834, USA.

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LABELLING

Carton



Bottle label

