AUSTRALIAN PRODUCT INFORMATION – ARICEPT® (DONEPEZIL HYDROCHLORIDE)

1. NAME OF THE MEDICINE

Donepezil hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ARICEPT film-coated tablets for oral administration are supplied containing 5 mg or 10 mg donepezil hydrochloride equivalent to 4.56 mg or 9.12 mg donepezil free base, respectively.

Excipient(s) with known effect

ARICEPT contains sugars (as lactose).

For the full list of excipients, see Section 6.1 List of excipients

3. PHARMACEUTICAL FORM

ARICEPT 5 mg film-coated tablets: white, round, film-coated, debossed tablets, marked 'ARICEPT' on one side and '5' on the other side.

ARICEPT 10 mg film-coated tablets: yellow, round, film-coated, debossed tablets, marked 'ARICEPT' on one side and '10' on the other side.

Not all presentations may be marketed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ARICEPT (donepezil hydrochloride) is indicated for the treatment of mild, moderate and severe Alzheimer's disease.

4.2 Dose and method of administration

Dosage

Adults/Elderly

Treatment should be initiated and supervised by a doctor experienced in the diagnosis and treatment of Alzheimer's Dementia. Individual response to donepezil cannot be predicted. Treatment should be continued for as long as a therapeutic benefit for the patient exists. Discontinuation of therapy should be considered where there is no longer evidence of a therapeutic effect, which should be assessed by periodic evaluations by the physician using input from the patient and caregiver.

The dosages of ARICEPT shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once daily. Although there is no statistically significant evidence that a greater treatment effect is obtained from the use of the 10 mg dose, there is a suggestion, based on analysis of group data that some additional benefits may accrue to some patients from the use of the higher dose.

Treatment is initiated at 5 mg/day (once-a-day dosing). ARICEPT tablets should be taken orally, in the evening, just prior to retiring. ARICEPT 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 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.

Dosage adjustment

Use in Renal & Hepatic Impairment

A similar dose schedule can be followed for patients with renal or hepatic impairment as clearance of donepezil hydrochloride is not significantly affected by these conditions.

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

Anaesthesia

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

Cardiovascular Conditions

Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g. bradycardia). The potential for this action may be particularly important to patients with 'sick sinus syndrome' or other supraventricular cardiac conduction conditions, such as sinoatrial or atrioventricular block. In the severe Alzheimer's disease studies, mild to moderate bradycardia was reported (see Section 4.8 Adverse effects (undesirable effects)).

There have been post-marketing reports of cardiac conduction conditions including atrioventricular block, QTc interval prolongation and Torsade de Pointes (see Section 4.5 Interactions with other medicines and other forms of interactions and Section 4.8 Adverse effects (undesirable effects)). Caution is advised in patients with pre-existing or family history of QTc prolongation, in patients being treated with drugs affecting the QTc interval, or in

patients with relevant pre-existing cardiac disease (e.g. uncompensated heart failure, recent myocardial infarction, bradyarrhythmias), or electrolyte disturbances (hypokalaemia, hypomagnesaemia). Clinical monitoring (ECG) may be required.

Gastrointestinal Conditions

Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk of developing ulcers, e.g. those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDs), should be monitored closely for symptoms of active or occult gastrointestinal bleeding. However, the clinical studies with ARICEPT showed no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Donepezil hydrochloride, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhoea, nausea and vomiting. Patients should be observed closely at the initiation of treatment and after dose increases.

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 have the potential to exacerbate or induce extrapyramidal symptoms.

Neuroleptic Malignant Syndrome (NMS)

NMS has been reported to occur very rarely in patients treated with donepezil, with or without concomitant antipsychotic medication. NMS is a potentially life-threatening condition characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels; additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.

If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, treatment should be discontinued immediately.

Pulmonary Conditions

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

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

Aggressive Behaviour

In patients with severe Alzheimer's disease, ARICEPT should be used with caution in patients at risk of aggression (see Section 4.8 Adverse effects (undesirable effects) - Severe Alzheimer's Disease).

Mortality in Subjects with Vascular Dementia

Three clinical trials of 6 months duration were conducted studying individuals meeting the NINDS AIREN criteria for probable or possible vascular dementia (VaD) and excluding patients with a diagnosis of Alzheimer's disease. In the first study, the mortality rates were 2/198 (1.0%) on ARICEPT 5 mg, 5/206 (2.4%) on ARICEPT 10 mg and 7/199 (3.5%) on placebo. In the second study, the mortality rates were 4/208 (1.9%) on ARICEPT 5 mg, 3/215 (1.4%) on ARICEPT 10 mg and 1/193 (0.5%) on placebo. In the third study, the mortality rates were 11/648 (1.7%) on ARICEPT 5 mg and 0/326 (0%) on placebo ($p<0.02$). The mortality rate for the three VaD studies combined in the ARICEPT 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 ARICEPT 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 ARICEPT group relative to placebo.

When Alzheimer's disease studies were pooled (n=4146), the mortality rate in the placebo group numerically exceeded that in the ARICEPT group. There is no evidence of an increased risk of mortality in the current approved indication of mild to moderately severe Alzheimer's disease.

Use in the elderly

See Section 4.4 Special warning and precautions for use - Mortality in Subjects with Vascular Dementia.

Paediatric use

ARICEPT is not recommended for use in children.

Effects on laboratory tests

No notable abnormalities in laboratory values associated with treatment were observed except for minor increases in serum concentrations of creatine kinase.

4.5 Interactions with other medicines and other forms of interactions

Drugs Highly Bound to Plasma Proteins

Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as frusemide, digoxin, and warfarin. ARICEPT at concentrations of 0.3-10 µg/mL did not affect the binding of frusemide (5 µg/mL), digoxin (2 ng/mL) and warfarin (3 µg/mL) to human albumin. Similarly, the binding of ARICEPT to human albumin was not affected by frusemide, digoxin and warfarin.

Drug-drug Interactions

Cases of QTc interval prolongation and Torsade de Pointes have been reported for donepezil (see Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects)). Caution is advised when donepezil is used in combination with other medicinal products known to prolong the QTc interval and clinical monitoring may be required. Examples include:

- Class IA antiarrhythmics (e.g. disopyramide)
- Class III antiarrhythmics (e.g. amiodarone, sotalol)
- Certain antidepressants (e.g. citalopram, escitalopram, amitriptyline)
- Other antipsychotics (e.g. phenothiazine derivatives, pimozide, ziprasidone)
- Certain antibiotics (e.g. clarithromycin, erythromycin, moxifloxacin).

Effects of ARICEPT on Other Medicines

No *in vivo* clinical trials have investigated the effect of ARICEPT on the clearance of drugs metabolised by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50-130 μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

Whether ARICEPT has any potential for enzyme induction is not known.

Formal pharmacokinetic studies evaluated the potential of ARICEPT for interaction with theophylline, cimetidine, warfarin and digoxin. No significant effects on the pharmacokinetics of these drugs were observed.

Effects of Other Medicines on ARICEPT

Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of these inhibitors is not known. In a study in healthy volunteers, ketaconazole increased mean donepezil concentrations by about 30%. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampicin, and phenobarbital) could increase the rate of elimination of ARICEPT.

Formal pharmacokinetic studies demonstrated that the metabolism of ARICEPT is not significantly affected by concurrent administration of digoxin or cimetidine.

Donepezil has the potential to interfere with medications having anticholinergic activity. There is also the potential for synergistic activity with concomitant treatment involving medications such as succinylcholine, other neuro-muscular blocking agents or cholinergic agonists or beta-blocking agents which have effects on cardiac conduction.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Donepezil had no effect on fertility in rats at oral doses up to 10 mg/kg/day (a tissue exposure equivalent to approximately twice that in humans at the maximum recommended clinical dose of 10 mg/day) in male and female rats based on AUC.

Use in pregnancy – Pregnancy Category B3

Teratology studies conducted in pregnant rats at oral doses up to 16 mg/kg/day and in pregnant rabbits at doses up to 10 mg/kg/day did not disclose any evidence for a teratogenic potential of donepezil. In rats this dose resulted in a systemic drug exposure in excess of human values. However, in rabbits the extent of systemic drug exposure is not known. Treatment of pregnant rats from late gestation to the end of lactation with an oral donepezil dose of 10 mg/kg/day

resulted in a slight increase in incidence of stillborn pups, and slightly reduced pup survival through day 4 postpartum.

There are no adequate or well-controlled studies in pregnant women. Donepezil hydrochloride should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in lactation

It is not known whether donepezil hydrochloride is excreted in human breast milk and there are no studies in lactating women. Excretion of donepezil and/or its metabolites into milk occurred after oral treatment of nursing rats, with milk concentrations similar to those in plasma. Therefore, women on donepezil should not breast feed.

4.7 Effects on ability to drive and use machines

Alzheimer's dementia may cause impairment of driving performance or compromise the ability to use machinery. Furthermore, donepezil can cause fatigue, dizziness and muscle cramps, mainly when initiating or increasing the dose. The ability of Alzheimer patients on donepezil to continue driving or operating complex machinery should be routinely evaluated by the treating physician.

4.8 Adverse effects (undesirable effects)

Most adverse events are mild in severity and transient in nature. The most common (incidence ≥5% and twice the frequency of placebo) were diarrhoea, muscle cramps, fatigue, nausea, vomiting and insomnia.

Other common adverse events (incidence ≥5% and ≥placebo) were headache, pain, accident, common cold, abdominal disturbance and dizziness. Cases of syncope, bradycardia, sinoatrial block and atrioventricular block were observed.

No notable abnormalities in laboratory values associated with treatment were observed except for minor increases in serum concentrations of creatine kinase.

Adverse events observed during long-term but not the short-term trials (incidence ≥5% and twice the frequency of placebo) included asthenia.

Adverse Events Leading to Discontinuation

The rate of discontinuation for the ARICEPT 5 mg/day treatment group was comparable to that of placebo-treated patients at approximately 5%. The rate of discontinuation of patients who received rapid dose escalations over 7 days from 5 mg/day to 10 mg/day, was higher at 13%. The most common signs and symptoms leading to discontinuation were nausea, diarrhoea and vomiting. For patients who did not discontinue, these signs and symptoms generally proved to be mild and transient, resolving in 1 to 2 days during continued use of the 10 mg/day dose. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration.

Adverse Events listed below were derived from the 15- and 30-week studies (see Section 5.1 Pharmacodynamic properties - Clinical trials) and a pivotal study of 14 weeks duration.

Table 1. Adverse Events Reported in Controlled Clinical Trials In at Least 2% of Patients Receiving ARICEPT and at a Higher Frequency than Placebo-treated Patients

	ARICEPT (n=747)	Placebo (n=355)
Body System/Adverse Event		
Percent of Patients with any adverse event	74	72
Body as a Whole		
Headache	10	9
Pain, various locations	9	8
Accident	7	6
Fatigue	5	3
Cardiovascular System		
Syncope	2	1
Digestive System		
Nausea	11	6
Diarrhoea	10	5
Vomiting	5	3
Anorexia	4	2
Haematological and Lymphatic System		
Ecchymosis	4	3
Metabolic and Nutritional		
Weight decrease	3	1
Musculoskeletal System		
Muscle Cramps	6	2
Arthritis	2	1
Nervous System		
Insomnia	9	6
Dizziness	8	6
Depression	3	<1
Abnormal Dreams	3	0
Somnolence	2	<1
Urogenital		
Frequent Urination	2	1

Other Adverse Events Observed During Clinical Trials

Treatment emergent signs and symptoms that occurred during three controlled clinical trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. All adverse events occurring at least twice and judged as possibly or definitely related to ARICEPT treatment are included, except for those already listed in Table 1. Events are classified by body system and include frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients.

Body as a Whole: generalised weakness, infection, influenza, assault

Cardiovascular System: vasodilation, hot flashes, hypotension, angina pectoris, hypertension

Digestive System: abdominal disturbance, constipation, faecal incontinence, bloating, stomach upset epigastric pain, eructation, gastrointestinal bleeding, increased appetite, flatulence, drooling, dry mouth, increased transaminases

Metabolic and Nutritional Disorders: dehydration, oedema of extremities

Musculoskeletal System: muscle weakness

Nervous System: agitation, anxiety, confusion, delusions, hallucinations, tremor, irritability, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, aphasia, coldness (localised), muscle spasm, hypokinesia, nervousness, paraesthesia, paranoia, wandering

Respiratory System: rhinitis, coughing, dyspnoea

Skin and Appendages: rash, abrasion, diaphoresis, pruritus

Special Senses: cataract, ear disorder, vision blurred

Urogenital System: urinary incontinence, urinary tract infection, nocturia.

Post-marketing experience

There have been post-marketing reports of hallucinations, agitation, aggressive behaviour, hypersexuality, pleurothotonus (Pisa syndrome), seizure, hepatitis, gastric ulcer, duodenal ulcer, gastrointestinal haemorrhage, abdominal pain, cholecystitis, heart block, electrocardiogram QT interval prolonged, polymorphic ventricular tachycardia including Torsade de Pointes (see Section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines and other forms of interactions), haemolytic anaemia, hyponatraemia, neuroleptic malignant syndromeand pancreatitis.

Severe Alzheimer's Disease

A total of 573 patients with severe Alzheimer's disease were treated in controlled clinical studies with ARICEPT. Of these patients, 441 (77%) completed the studies. The mean duration of treatment for all ARICEPT groups was 148.4 days (range 1-231 days).

The incidence profile for adverse events for severe Alzheimer's disease was similar to that of mild to moderate Alzheimer's disease.

In controlled clinical trials in severe Alzheimer's disease, the rate of discontinuation due to adverse events was 11.3% in patients treated with ARICEPT compared to 6.7% in the placebo group. No individual adverse event led to discontinuation in greater than 2% of patients. Other less common adverse events leading to discontinuation included diarrhoea, nausea, vomiting, urinary tract infection, decreased appetite, and aggression.

The most common adverse events, defined as those occurring at a frequency of at least 5% in patients and twice the placebo rate, were diarrhoea, nausea, and aggression. The incidence of aggression was increased in men, occurring in 11.2% of men who received donepezil, compared with 3.1% who received placebo. In women, aggression was seen in 2.9% of donepezil patients versus 2.1% of placebo patients. Overall, the majority of adverse events were judged by the investigators to be mild or moderate in intensity.

Adverse events presented by age (<75 years and ≥75 years) and treatment are shown in Table 2. Overall, the incidence of common adverse events was similar between age groups by treatment. The incidence of falls increased with age in both treatment groups, as did the incidence of urinary tract infections and vomiting. The incidence of diarrhoea did not correlate with age, but was related to treatment. The incidence of nausea was less in the ≥75-year age group but related to treatment.

Table 2. Adverse event data in the severe studies stratified by age

Body System/ Adverse Event	Patients aged <75 years		Patients aged ≥75 years	
	ARICEPT (n=158)	Placebo (n=114)	ARICEPT (n=415)	Placebo (n=351)
Gastrointestinal disorders				
Diarrhoea	10.1	3.5	10.4	4.3
Nausea	7.0	3.5	5.1	2.3
Vomiting	5.7	3.5	8.2	4.0
Constipation	5.1	3.5	4.1	3.7
Infections and infestations				
Nasopharyngitis	10.1	4.4	7.5	6.8
Urinary tract infection	4.4	4.4	9.4	8.0
Injury, poisoning and procedural complications				
Fall	8.9	5.3	10.6	10.0
Nervous system disorders				
Headache	7.0	5.3	4.3	2.3
Psychiatric disorders				
Aggression	7.0	5.3	4.3	1.4
Agitation	5.1	10.5	6.7	5.1

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Symptoms

Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterised by severe nausea, vomiting, miosis, lacrimation, salivation, sweating, flushing, bradycardia, involuntary urination and/or defecation, bronchospasm, increased bronchial secretions, respiratory depression, collapse and convulsions/seizures. Hypotension following overdose could be severe leading to cardiovascular collapse or shock. Abdominal pain, diarrhoea, increased micturition, diaphoresis, vertigo, fasciculations, tremors, agitation, lethargy, syncope and coma may occur. Various dysrhythmias, primarily heart block, may theoretically occur due to cholinergic effects. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Due to its high degree of selectivity for AChE in the CNS

and less peripheral selectivity, overdoses would be expected to exhibit more CNS-related symptomatology, including extrapyramidal effects.

Overdoses of 45 mg and 50 mg in two elderly patients resulted in minimal effects, predominately gastrointestinal, and in one case persistent bradycardia (HR in the 40's) both with uneventful recoveries.

Treatment

As in any case of overdose, general supportive measures should be utilised. Cholinesterase activity may be depressed and should be monitored in plasma (pseudocholinesterase) and red blood cells. Monitor ECG following significant exposures. Monitor pulse oximetry and/or arterial blood gases and obtain a chest radiograph in patients with pulmonary symptoms. 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. Consider administration of activated charcoal in the event of a potentially toxic ingestion. Activated charcoal is most effective when administered within one hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. It is not known whether donepezil and/or its metabolites can be removed by dialysis (haemodialysis, peritoneal dialysis, or haemofiltration). Emesis is not recommended because of the potential for CNS depression and seizures.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

It has been demonstrated that Alzheimer's disease is associated with a relative decrease in the activity of the cholinergic system in the cerebral cortex and other areas of the brain.

Studies suggest that donepezil hydrochloride exerts its therapeutic effect by enhancing cholinergic function in the central nervous system. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of acetylcholinesterase.

Mechanism of action

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

In patients with Alzheimer's Dementia participating in clinical trials, administration of single daily doses of 5 mg or 10 mg 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 correspond closely to the effects in the cerebral cortex. In addition, significant correlation was demonstrated between plasma levels of donepezil hydrochloride, AChE inhibition and change in ADAS-cog, a sensitive and well validated scale which examines cognitive performance – including memory, orientation, attention, reason, language and praxis.

Clinical trials

Mild to Moderately Severe Alzheimer's disease

Studies of Less Than One Year Duration

The effectiveness of ARICEPT in the treatment of Alzheimer's disease has been demonstrated by two randomised, double-blind, placebo-controlled studies (15- and 30-week) in which 436 patients were treated with ARICEPT. Criteria for inclusion were patients with mild to moderately severe Alzheimer's disease (diagnosed by NINCDS and DSM III-R criteria, Mini-Mental State Examination ≥10 and ≤26 and Clinical Dementia Rating of 1 or 2).

Study Outcome Measures: In each study, the effectiveness of treatment with ARICEPT was evaluated using a dual outcome assessment strategy.

The ability of ARICEPT to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment. Elderly normal adults may score as low as 0 or 1, but it is not unusual for non-demented adults to score slightly higher.

The patients recruited as participants in each study had mean scores on the Alzheimer's Disease Assessment Scale (ADAS-cog) of approximately 26 units, with a range from 4 to 61. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's disease suggests that they gain 6 to 12 units a year on the ADAS-cog. However, lesser degrees of change are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in ARICEPT trials was approximately 2 to 4 units per year.

The ability of ARICEPT to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC plus. Unlike ADAS-cog, the CIBIC plus is not a single instrument nor is it a standardised instrument like the ADAS-cog. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC plus evaluations from other clinical trials. The CIBIC plus used in ARICEPT trials was a semi-structured instrument that was intended to examine four major areas of patient function: General, Cognitive, Behavioural and Activities of Daily Living. It represents the assessment of a skilled clinician based upon his/her observations at an interview with the patient, in combination with information supplied by a caregiver familiar with the behaviour of the patient over the interval rated. The CIBIC plus is scored as a seven point categorical rating, ranging from a score of 1, indicating 'markedly improved', to a score of 4, indicating 'no change' to a score of 7, indicating 'markedly worse'.

The CIBIC plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods.

Thirty-Week Study

In a study of 30 weeks duration, 473 patients were randomised to receive single daily doses of placebo, 5 mg/day or 10 mg/day of ARICEPT. The 30-week study was divided into a 24-week double-blind active treatment phase followed by a 6-week single-blind placebo washout period. The study was designed to compare 5 mg/day or 10 mg/day fixed doses of ARICEPT to placebo. However, to reduce the likelihood of cholinergic effects, the 10 mg/day treatment was started following an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all three dose groups over the 30 weeks of the study. After 24 weeks of treatment, the mean differences in the ADAS-cog change scores for ARICEPT treated patients compared to the patients on placebo were 2.8 and 3.1 units for the 5 mg/day and 10 mg/day treatments, respectively. These differences were statistically significant. While the treatment effect size may appear to be slightly greater for the 10 mg/day treatment, there was no statistically significant difference between the two active treatments.

Following 6 weeks of placebo washout, scores on the ADAS-cog for both the ARICEPT treatment groups were indistinguishable from those patients who had received only placebo for 30 weeks. This suggests that the beneficial effects of ARICEPT abate over 6 weeks following discontinuation of treatment and do not represent a change in the underlying disease. There is no evidence of a rebound effect 6 weeks after abrupt discontinuation of therapy.

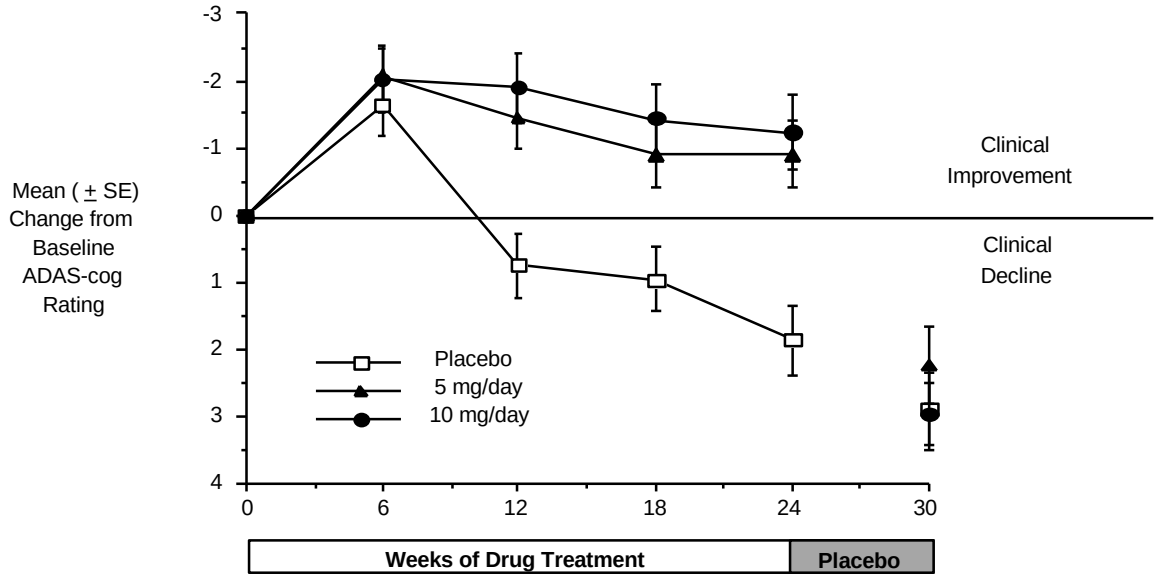


Figure 1. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing 24 Weeks of Treatment

Figure 2 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained the measure of improvement in ADAS-cog score shown on the X axis. Three change scores, (7-point and 4-point reductions from baseline or no change in score) have been identified for illustrative purposes and the percent of patients in each group achieving that result is shown in this inset table.

The curves demonstrate that both patients assigned to placebo and ARICEPT have a wide range of responses, but that the active treatment groups are more likely to show greater improvements. A curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon or shifted to the right of the curve for placebo, respectively.

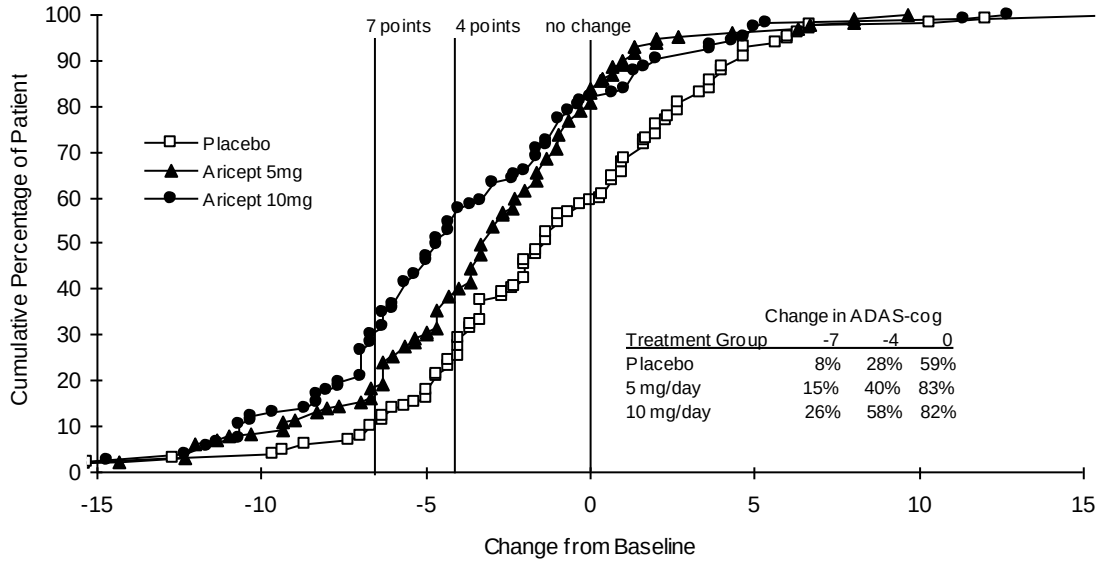


Figure 2. Cumulative Percentage of Patients Completing 24 Weeks of Double-blind Treatment with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients who Completed the Study were: Placebo 80%, 5 mg/day 85% and 10 mg/day 68%

Effects on the CIBIC plus: Figure 3 is a histogram of the frequency distribution of CIBIC plus scores attained by patients assigned to each of the three treatment groups who completed 24 weeks of treatment. The mean drug-placebo differences for these groups of patients were 0.35 units and 0.39 units for 5 mg/day and 10 mg/day of ARICEPT, respectively. These differences were statistically significant. There was no statistically significant difference between the two active treatments.

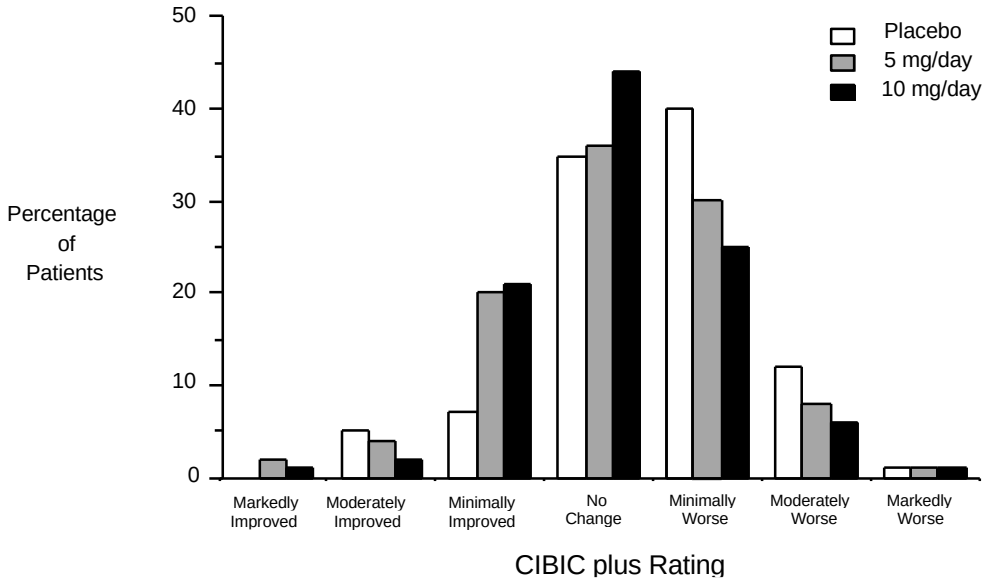


Figure 3. Frequency Distribution of CIBIC plus Scores at Week 24

Fifteen-Week Study

In a study of 15 weeks duration, patients were randomised to receive single daily doses of placebo or either 5 mg/day or 10 mg/day of ARICEPT for 12 weeks, followed by a 3-week placebo washout period. As in the 30-week study, to avoid acute cholinergic effects, the 10 mg/day treatment followed an initial 7-day treatment with 5 mg/day doses.

Effects on the ADAS-Cog: Figure 4 illustrates the time course of the change from baseline in ADAS-cog scores for all three dose groups over the 15 weeks of the study. After 12 weeks of treatment, the differences in mean ADAS-cog change scores for the ARICEPT treated patients compared to the patients on placebo were 2.7 and 3.0 units each, for the 5 and 10 mg/day ARICEPT treatment groups respectively. These differences were statistically significant. The effect size for the 10 mg/day group may appear to be slightly larger than that for 5 mg/day. However, the differences between active treatments were not statistically significant.

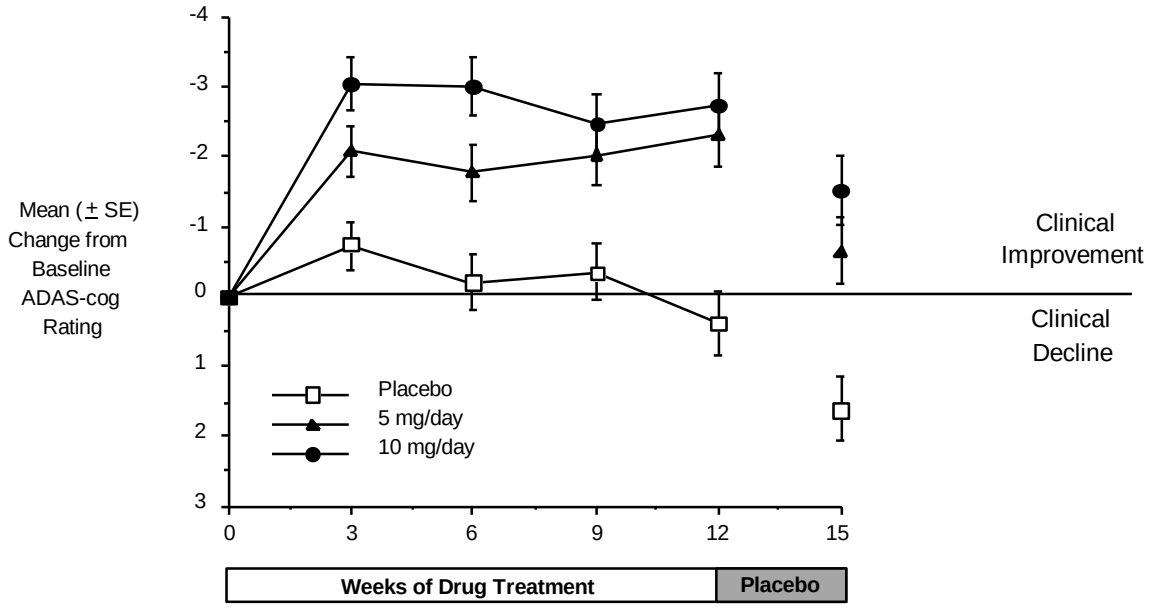


Figure 4. Time-course of the Change from Baseline in ADAS-cog Score for Patients Completing the 15-week Study

Following 3 weeks of placebo washout, scores on the ADAS-cog for both the ARICEPT treatment groups increased, indicating that discontinuation of ARICEPT resulted in a loss of its treatment effect. The duration of this placebo washout period was not sufficient to characterise the rate of loss of the treatment effect, but the 30-week study (see above) demonstrated that treatment effects associated with the use of ARICEPT abate within 6 weeks of treatment discontinuation.

Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who attained the measure of improvement in ADAS-cog score shown on the X axis. The same three change scores, (7-point and 4-point reductions from baseline or no change in score) as selected for the 30-week study have been used for this illustration. The percentages of patients achieving those results are shown in the inset table.

As observed in the 30-week study, the curves demonstrate that patients assigned to either placebo or to ARICEPT have a wide range of responses, but that the ARICEPT treated patients are more likely to show the greater improvements in cognitive performance.

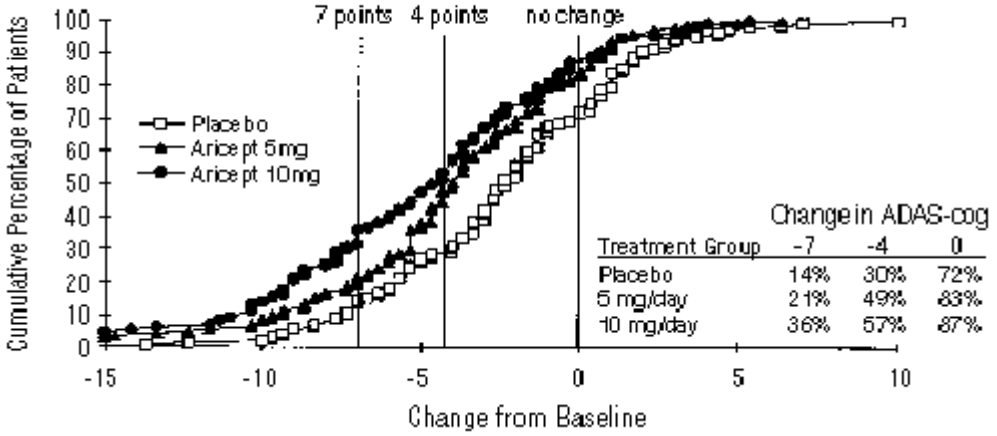


Figure 5. Cumulative Percentage of Patients with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients Within Each Treatment Group Who Completed the Study Were: Placebo 93%, 5 mg/day 90% and 10 mg/day 82%

Effects on the CIBIC plus: Figure 6 is a histogram of the frequency distribution of CIBIC plus scores attained by patients assigned to each of the three treatment groups who completed 12 weeks of treatment. The differences in mean scores for ARICEPT treated patients compared to the patients on placebo at Week 12 were 0.36 and 0.38 units for the 5 mg/day and 10 mg/day treatment groups, respectively. These differences were statistically significant.

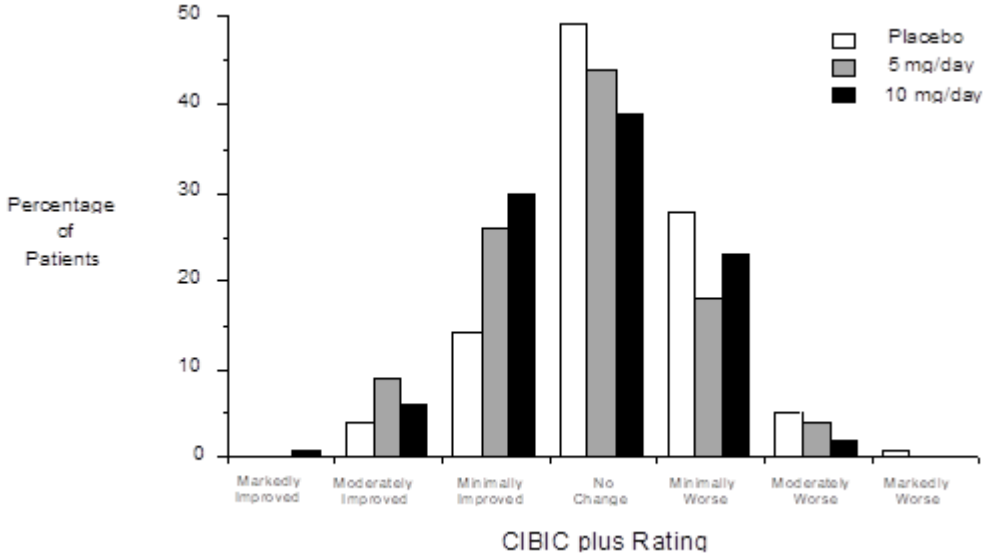


Figure 6. Frequency Distribution of CIBIC plus Scores at Week 12

In both studies, patient age, sex and race were not found to predict the clinical outcome of ARICEPT treatment.

Studies of Greater Than One Year Duration

The effectiveness of ARICEPT in the treatment of Alzheimer's disease has been demonstrated by two randomised, double-blind, placebo-controlled studies (54-week) in which 356 patients were treated with ARICEPT.

Fifty Four-Week Study #1

In a 54-week double-blinded study, patients were randomised to receive either placebo or 5 mg ARICEPT once daily for 28 days followed by 10 mg once daily for the remainder of the study. Criteria for inclusion included: diagnosis of mild to moderate Alzheimer's disease (DSM-IV, 290.00 or 290.10 of the NINCDS criteria), Clinical Dementia Rating (CDR)=1 or 2, MMSE of 12–20, retention of at least 8 Instrumental Activities of Daily Living (IADLs) and at least 5 basic Activities of Daily Living (ADLs) and a modified Hachinski score ≤4. The intent to treat analysis consisted of 207 ARICEPT-treated patients and 208 placebo patients.

Study outcome measure: The primary outcome measure for assessment of efficacy of ARICEPT was based upon attrition from the study due to clinically evident functional decline. Patients were assessed at 6-week intervals. Attrition was determined by the investigator as follows: 1) a clinically significant decline in ability to perform one or more basic ADL which were present at baseline, 2) a clinically significant decline in ability to perform 20% or more of IADLs which were present at baseline, or 3) an increase in CDR score compared to baseline.

Basic ADL items are defined by the patient's ability in toileting, feeding, dressing, personal hygiene/grooming, bathing and walking. Instrumental ADLs involve the assessment of 10 items: use of telephone, household tasks, using household appliances, managing money, shopping, food preparations, ability to get around inside and outside home, hobbies and leisure activities, handling personal mail, and grasp of situations or explanations. The CDR assesses six cognitive and behavioural domains: memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care.

Time to attrition: In the Kaplan-Meier analysis, ARICEPT treatment produced significantly greater preservation of function, as determined by time to attrition, than placebo as illustrated in Figure 7 below. By using Log-rank and Wilcoxon tests to compare survival distribution of time to attrition, the median time to attrition was more than 357 days (lower limit of the 95% CI=280) for ARICEPT-treated patients, whereas the median time to attrition for placebo-treated patients was 208 days (95% CI=[165, 252]). Both Log-rank and Wilcoxon tests indicated that the survival curves for the two treatment groups were significantly different (p=0.0019 and p=0.0051, respectively).

The hazard ratio (ARICEPT/placebo) was 0.62 indicating the relative risk of clinically evident function decline for patients who received ARICEPT was approximately 62% of that of patients who received placebo.

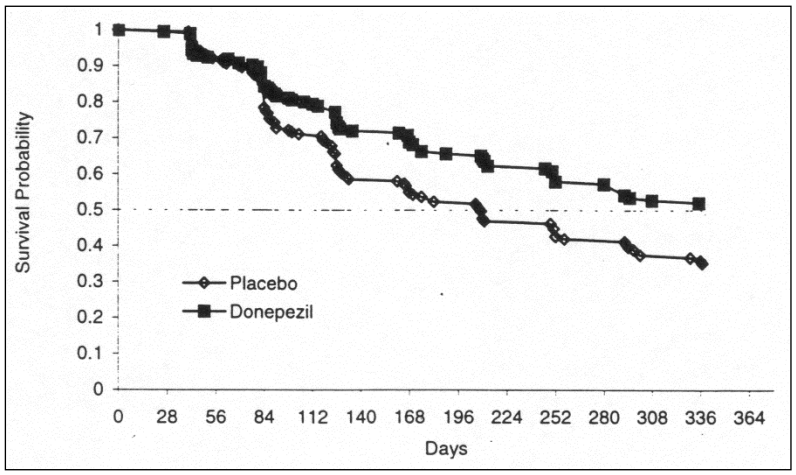


Figure 7. Estimated Probabilities of Time to Attrition by Investigator from Kaplan-Meier Survival Function Analyses: Intent-to-treat Population

Fifty Four-Week Study #2

In a study of 54 weeks duration, patients were randomised to receive either placebo or 5 mg ARICEPT once daily, which was increased to 10 mg once daily at day 29 and maintained until the end of the study. Criteria for inclusion included a diagnosis of mild to moderate Alzheimer's disease (DSM-IV, NINCDS-ADRDA criteria and MMSE of 10–26).

Study outcome measure: The primary efficacy variable was the Gottfries, Bråne and Steen (GBS) scale, which assesses global function. It is based on a semi-structured interview with the patient's caregiver. This 27-item scale assesses four domains including intellectual function (12 items), motor function (basic ADLs – 6 items), emotional function (3 items) and behavioural symptoms characteristic for dementia syndromes (6 items).

Global function: On the GBS scale, ARICEPT-treated patients showed a trend to improvement compared to placebo patients at endpoint analysis (p=0.054). By intention to treat analysis of observed cases, ARICEPT-treated patients performed significantly better than placebo patients at 24, 36 and 52 weeks.

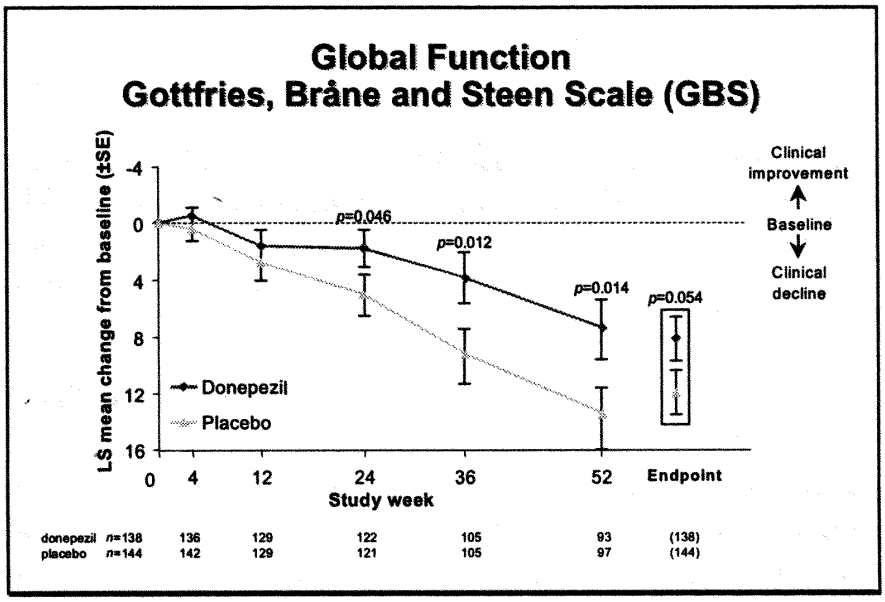


Figure 8. LS Mean Change from Baseline for GBS Total Score by Week and Treatment Group – ITT population (Observed Cases and Week 52 LOCF)

Quality of Life

Although a trend of improvement on quality of life (QOL) measures was observed in clinical trials of ARICEPT treated patients, there were large variances in QOL scores. These are consistent with observations regarding quality of life assessments in Alzheimer's disease patients generally. It has been demonstrated that Alzheimer's disease patients' opinions will be influenced by the day-to-day fluctuations in their illness (often quite substantial), leading to similar day-to-day variability in their perception of quality of life. Alzheimer's disease patients may also be unreliable sources of information on quality of life because of significant losses in executive functions such as judgement and insight that are key to obtaining meaningful assessments.

Severe Alzheimer's Disease

The effectiveness of ARICEPT in the treatment of severe Alzheimer's disease has been demonstrated by three randomised, double-blind, placebo-controlled studies (one 26-week and two 24-week) in which 517 patients were randomised to receive ARICEPT. Criteria for inclusion were patients with severe Alzheimer's disease (diagnosed by NINCDS-ADRDA and DSM IV criteria, Mini-Mental State Examination (MMSE) and a Functional Assessment Staging (FAST).

Study Outcome Measures: In each study, the effectiveness of treatment with ARICEPT was evaluated using a combination of assessments of cognition, global function, activities of daily living (daily function), and behavioural and psychological symptoms.

Cognition

SIB: The primary tool in the three studies used to assess cognition was the Severe Impairment Battery (SIB). The SIB evaluates cognitive dysfunction over nine domains (social interactions,

memory, orientation, language, attention, praxis, visuospatial, construction and orienting to name). Total scores range from 1 to 100, and lower scores indicate greater impairment.

MMSE: Cognitive changes over time are often assessed using the Mini-Mental State Examination (MMSE), a 30-point test. Lower scores indicate a greater degree of impairment, and scores ≤12 points or ≤10 points have been used to define the severe stages of dementia. The MMSE was used in two of the studies as a secondary endpoint.

Global function

CIBIC plus: Similar to the studies in mild to moderate Alzheimer's disease, the Clinician's Interview Based Impression of Change with caregiver input (CIBIC plus) was used as a primary endpoint to assess global function for two of the three studies.

CGI-I: In one of the studies, the Clinical Global Impression of Improvement (CGI-I) was used as a primary endpoint as a measure of global function. Similar to CIBIC plus, the physician rates the patient's condition relative to baseline on a 7-point Likert-like scale, with scores of 1-3 representing degrees of improvement, 4 representing no change, and 5-7 representing degrees of worsening.

Activities of daily living

ADCS-ADL severe: To assess activities of daily living (ADL), all three studies used the modified ADCS-ADL inventory for severe Alzheimer's disease (ADCS-ADL-severe). This is based on an interview with the caregiver and measures the patient's most usual and consistent ability to perform basic and instrumental ADL during the previous 4 weeks. The scale ranges from 0 to 54, with lower scores indicating greater functional impairment.

Behavioural and psychological symptoms

Two scales were used to assess behavioural and psychological symptoms: the neuropsychiatric inventory (NPI) and the Behavioural Pathology in Alzheimer's disease scale (BEHAVE-AD).

NPI: The 12 item NPI, used in two studies, is based on the caregiver's assessment of the frequency and severity of a range of mood and behavioural disturbances since the last evaluation. Total NPI scores range from 0 (best score) to 144 (worst score).

BEHAVE-AD: The BEHAVE-AD scale, used in 1 study, is similarly based on the caregiver's assessment of the presence and magnitude of a range of neuropsychiatric symptoms over the past 2 weeks. Total BEHAVE-AD scores range from 0 (best score) to 78 (worst score).

Overall efficacy results from the three severe studies

Overall, donepezil-treated patients significantly benefited compared with placebo for the outcome measures of SIB scores, CIBIC plus scores, ADCS-ADL-severe scores and MMSE. Table 3 shows the pooled efficacy results, which have also been stratified by age. There was no significant age by treatment interaction for any of the measures in this pooled analysis. It is important to note that efficacy results stratified by age are a sub-group analysis. The studies were not powered to demonstrate efficacy in these subgroup analyses, and the results must be interpreted with caution.

In addition, in the three severe Alzheimer's disease studies, SIB scores, CIBIC plus/CGI-I scores and ADCS-ADL-severe scores were also not influenced by gender or by the diagnosis as probable or possible Alzheimer's disease.

Table 3. Efficacy results at month 6 (change from baseline) for primary and secondary endpoints. Data pooled from the three severe studies

Study domain	IIT-LOCF analysis				ITT-OC analysis			
	Donepezil 10 mg N LS Mean Change/SE	Placebo N LS Mean Change/SE	Treatment difference LS mean 95% CI	P-value	Donepezil 10 mg N LS Mean Change/SE	Placebo N LS Mean Change/SE	Treatment difference LS mean 95% CI	P-value
SIB								
All subjects	367 2.6 (0.9)	363 -3.7 (0.9)	6.4(4.5, 8.2)	<0.001	277 3.3 (0.9)	297 -3.4 (0.9)	6.7 (4.6, 8.8)	<0.001
≤74 years	81 1.0 (1.2)	75 -7.6 (1.3)	8.6 (5.2, 12.1)	<0.001	64 1.1 (1.3)	59 -5.8 (1.3)	6.8 (3.1, 10.5)	<0.001
≥75 years	286 3.0 (1.1)	288 -2.8 (1.0)	5.8 (3.7, 8.0)	<0.001	213 3.9 (1.0)	238 -2.9 (1.0)	6.8 (4.3, 9.2)	<0.001
CIBIC + score								
All subjects	259 4.0 (0.1)	259 4.3 (0.1)	-0.3 (-0.5, -0.1)	0.003	179 4.0 (0.1)	197 4.3 (0.1)	-0.3 (-0.6, -0.1)	0.004
≤74 years	77 4.1 (0.1)	73 4.5 (0.1)	-0.4 (-0.8, -0.1)	0.027	60 4.0 (0.1)	57 4.5 (0.2)	-0.5 (-0.9, 0.0)	0.034
≥75 years	182 4.0 (0.1)	186 4.3 (0.1)	-0.3 (-0.5, 0.0)	0.029	119 4.0 (0.1)	140 4.3 (0.1)	-0.3 (-0.6, 0.0)	0.036
ADC-ADL-sev								
All subjects	350 -1.2 (0.8)	349 -2.2 (0.8)	1.0 (0.1, 1.9)	0.025	270 -0.9 (0.9)	292 -1.7 (0.9)	0.8 (-0.1, 1.8)	0.087
≤74 years	76 -1.1 (0.7)	72 -3.0 (0.7)	1.8 (-0.2, 3.8)	0.072	59 -1.0 (1.1)	56 -2.1 (1.1)	1.1 (-1.1, 3.3)	0.339
≥75 years	274 -1.1 (0.8)	277 -1.9 (0.8)	0.8 (-0.2, 1.8)	0.104	211 -0.8 (0.8)	236 -1.6 (0.8)	0.8 (-0.3, 1.9)	0.168
MMSE								
All subjects	239 1.0 (0.4)	245 0.0 (0.4)	1.0 (0.4, 1.6)	0.001	206 1.1 (0.4)	217 0.0 (0.4)	1.1 (0.5, 1.7)	0.001
≤74 years	49 0.0 (0.8)	45 -1.0 (0.8)	1.0 (-0.2, 2.3)	0.113	38 -0.1 (0.8)	42 -0.9 (0.8)	0.8 (-0.6, 2.2)	0.255
≥75 years	190 1.1 (0.4)	200 0.1 (0.4)	1.0 (0.3, 1.7)	0.004	168 1.3 (0.4)	175 0.1 (0.4)	1.2 (0.5, 1.9)	0.001
NPI								
All subjects	262 -2.2 (1.2)	251 -2.1 (1.2)	-0.1 (-2.7, 2.6)	0.959	205 -2.9 (1.0)	216 -3.5 (1.0)	0.6 (-2.2, 3.3)	0.694
≤74 years	46 -0.3 (2.6)	51 4.3 (2.5)	-4.6 (-11.7, 2.4)	0.195	38 -0.1 (2.6)	42 1.4 (2.5)	-1.5 (-8.8, 5.7)	0.676
≥75 years	216 -2.5 (1.0)	200 -3.6 (1.0)	1.1 (-1.7, 4.0)	0.432	167 -3.6 (1.1)	174 -4.7 (1.0)	1.1 (-1.9, 4.0)	0.468

NOTE:
(1). L.S MEAN and p-values based on Mixed models with Treatment, Baseline as fixed effects and STUDY as random effect.
(2). CIBIC+ was not used in the 26-week study, NPI was only used in one of the 24-week studies, and post baseline MMSE was not evaluated in one of the 24-week studies.

Individual study description and efficacy results for the 26-week and the two 24-week studies are shown below.

Twenty-Six-Week Study

In a study of 26 weeks duration, safety and efficacy were evaluated by randomising 249 patients to receive a single daily dose of placebo or 10 mg/day of ARICEPT. To reduce the likelihood of cholinergic effects, treatment was initiated at 5 mg/day for 4 weeks, then treatment was increased to 10 mg/day, based on clinical judgement. At any time during the study, the dose of donepezil could be reduced from 10 mg to 5 mg daily based on the investigator's assessment of tolerability. The primary endpoints for this study were the effects on the SIB and the ADCS-ADL-severe scores.

After 26 weeks of treatment, the mean difference in the SIB change scores for ARICEPT-treated patients compared with placebo was 5.7 points. The difference was statistically significant (p=0.008). For the effect on the ADCS-ADL-severe score, the ARICEPT-treated patients also showed significantly less decline (-1.4 points) than the patients on placebo (-3.0 points) (p=0.029). In this study MMSE, NPI, and CGI-I were used as secondary endpoints. Donepezil treated patients showed a significantly greater mean improvement (1.5 points) than placebo-treated patients (0.1 points) in the MMSE score (p=0.008). There was no statistically significant difference between the treatment groups for the NPI (p=0.426). The percentage of patients showing any degree of improvement in the CGI-I was 53.2% for donepezil-treated patients and 38.3% in the placebo (p=0.055), while the distribution for patients in the worsened category was greater for the placebo treated-patients (25.2% placebo versus 20.7% donepezil-treated).

For those patients who discontinued, placebo-treated patients withdrew slightly later than donepezil-treated patients (median time to withdrawal 72 days following placebo compared to 70 days following donepezil). More patients remained on placebo treatment (82.5%) than on donepezil treatment (74.2%). The difference was not statistically significant (Table 4).

Table 4. Summary of patient disposition

	Treatment group	
	Donepezil	Placebo
Assigned to Study Treatment 249*		
Treated	128	120
Completed the study	95 (74.2%)	99 (82.5%)
Discontinued the study at:		
0-3 weeks	5 (3.9%)	2 (1.7%)
4-6 weeks	3 (2.3%)	5 (4.2%)
7-12 weeks	10 (7.8%)	4 (3.3%)
13-18 weeks	6 (4.7%)	5 (4.2%)
19 weeks to study end	9 (7.0%)	5 (4.2%)
Total discontinued early	33 (25.8%)	21 (17.5%)
Reason for discontinuation**		
Patiend died****	8 (6.3%)	12 (10.0%)
Related to study drug		
Adverse event	6 (4.7%)	1 (0.8%)

	Treatment group	
	Donepezil	Placebo
Not related to study drug		
Adverse event	14 (10.9%)	7 (5.8%)
Other	3 (2.3%)	0 (0.0%)
Patient defaulted***	2 (1.6%)	1 (0.8%)

*1 of the 249 patients was randomized but did not take study medication.

**Figures are given only for patients who received study medication.

***Patient withdrew consent or was lost to follow-up

****18 additional patient deaths are in the safety database. Of these 18 patients, 14 are listed as discontinued for AE (and subsequently died), and four are listed as completing the study (and subsequently died). One of these 18 patients died 35 days after discontinuation from the study.

Twenty-Four-Week Study#1

In a study of 24 weeks duration, 343 patients were randomised to receive single daily doses of placebo or 10 mg/day of ARICEPT. Patients received 5 mg for the first 6 weeks of the study and then 10 mg for the remainder of the double-blind period. At any time during the study, the dose of donepezil could be reduced from 10 mg to 5 mg daily based on the investigator's assessment of tolerability. The primary endpoints for this study were the effects on the SIB and the CIBIC plus scores.

After 24 weeks of treatment, the mean difference in the SIB change scores for ARICEPT-treated patients compared with was 5.3 points (p=0.0001). The percentage of patients showing any degree of improvement on their CIBIC plus score was 27.8% for donepezil-treated patients and 22.7% for the placebo group (p=0.09). For the other outcome measures donepezil-treated patients showed a significantly greater mean improvement (0.7 points) than placebo-treated patients (0.0 points) in the MMSE score (p=0.0267). There were no statistically significant differences between the treatment groups for the ADCS-ADL-sev or NPI scales.

For those patients who discontinued, donepezil-treated patients withdrew somewhat sooner (median time 65 days) than placebo-treated patients (median time 75 days). Statistically significantly more patients remained on treatment in the placebo-treated group (76.0%) than in the donepezil-treated group (66.5%) (Table 5).

Table 5. Summary of patient disposition

	Treatment group	
	Donepezil	Placebo
Total randomized	176	167
Completed the study	117 (66.5%)	127 (76.0%)
Discontinued the study at:		
0-3 weeks	14 (8.0%)	5 (3.0%)
4-6 weeks	5 (2.8%)	7 (4.2%)
7-12 weeks	21 (11.9%)	12(7.2%)
13-18 weeks	10 (5.7%)	11 (6.6%)
19 weeks to study end	9 (5.1%)	5 (3.0%)
Total discontinued early	59 (33.5%)	40 (24.0%)
Reason for discontinuation		
Adverse event/intercurrent illness[a]	34 (19.3%)	18 (10.8%)
Investigator/sponsor request	5 (2.8%)	3 (1.8%)
Medication noncompliance	2 (1.1%)	3 (1.8%)
Protocol violation	0 (0.0%)	2 (1.2%)
Patient entered nursing home facility	5 (2.8%)	5 (3.0%)
Other	13 (7.4%)	9 (5.4%)

[a]Including two deaths in the donepezil group and eight deaths in the placebo group.

Long term efficacy data are provided by an open label extension of this study. After 36 weeks of donepezil treatment, the mean SIB value remained at or near the baseline level, suggesting no further decline in cognitive functions.

Twenty-Four-Week Study#2

In a study of 24 weeks duration, 325 patients were randomised to receive single daily doses of placebo, low dose donepezil or high dose donepezil. For the low dose 3 mg/daily were administered for the first 2 weeks, then this was increased to 5 mg/day. For the high does group, 3 mg/day was administered for the first 2 weeks, then 5 mg/day were administered for 4 weeks, and from week 6 onwards, 10 mg/day were administered. Patients assigned to the 10 mg group needed to be able to tolerate the 10 mg/day dose to continue with the study. Patients who could not tolerate this dose were discontinued from the study. The primary endpoints used were the SIB score and the CIBIC-plus score.

After 24 weeks of treatment, the ARICEPT-treated patients showed a mean improvement in SIB (6.7 points in the 5 mg group and 8.9 points in the 10 mg group) compared with placebo. At both dose levels the difference was statistically significant ($p<0.0001$ at each level). For the effect on global function, the percentage of patients showing any degree of improvement was 46.7% in the group treated with 10 mg of donepezil, 32.3% for the 5 mg donepezil-treated group and 23.8% for placebo treated-patients. The difference was significantly different for the 10 mg group ($p=0.003$), but not for the 5 mg group ($p=0.151$). There were no statistically significant differences between the treatment groups for the ADCS-ADL-sev and BEHAVE-AD scales.

More patients on 5 mg remained on treatment (87.1%) than on 10 mg (79.2%) or on placebo (80.0%), although the difference was not statistically significant (Table 6). For those patients who discontinued, patients withdrew soonest for the 5 mg group (median time 55 days) followed by the 10 mg group (median time 65 days) followed by the placebo group (median time 83 days).

Table 6. Summary of patient disposition

	Treatment group		
	Placebo	Donepezil 5mg	Donepezil 10mg
Number of subjects enrolled	105	101	96
Completed the study	84 (80.0%)	88 (87.1%)	76 (79.2%)
Discontinued the study at:			
0-3 weeks	0	4 (4.0%)	3 (3.1%)
4-6 weeks	3 (2.9%)	2 (2.0%)	5 (5.2%)
7-12 weeks	8 (7.6%)	2 (2.0%)	9 (9.4%)
13-18 weeks	10 (9.5%)	4 (4.0%)	2 (2.1%)
19 weeks to study end	0	1 (1.0%)	1 (1.0%)
Total discontinued early	21 (20.0%)	13 (12.9%)	20 (20.8%)
Reason for discontinuation*			
Drug free period for 3 weeks or more	1 (1.0%)	0	0
Change in career	0	1 (1.0%)	3 (3.1%)
Difficulties for career	4 (3.8%)	1 (1.0%)	1 (1.0%)
Symptom aggravation	1 (1.0%)	0	2 (2.1%)
Side effects	1 (1.0%)	3 (3.0%)	4 (4.2%)
Complication emergence & exacerbation	2 (1.9%)	1 (1.0%)	2 (2.1%)
Wish to stop	3 (2.9*%)	1 (1.0%)	3 (3.1%)
Failure to attend hospital	0	1 (1.0%)	1 (1.0%)
Moved house	1 (1.0%)	0	0
Admitted to hospital & evaluation difficult	3 (2.9%)	2 (2.0%)	1 (1.0%)
Other	5 (4.8%)	3 (3.0%)	3 (3.1%)

* There were two deaths in the donepezil 5 mg group, two in the donepezil 10 mg group, and one in the placebo group. One of the two deaths in the donepezil 5 mg group occurred after the 30-day post-study period, but the onset of the cause of death was during the study period.

5.2 Pharmacokinetic properties

Absorption

Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3 to 4 hours. Oral administration of ARICEPT produces highly predictable plasma concentrations with 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 the 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.

Neither food nor time of administration (morning versus evening dose) affect the absorption of donepezil hydrochloride.

Distribution

The steady state volume of distribution is 12 L/kg. Donepezil hydrochloride is approximately 96% bound to human plasma proteins. 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 and/or its metabolites may persist in the body for more than 10 days.

The average CSF:plasma ratio for both doses, expressed as a percent of the concentration in plasma, was 15.7%.

Metabolism and Excretion

Donepezil is both excreted in the urine intact and extensively metabolised to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Three of the human metabolites of donepezil have not undergone extensive safety tests in animals. These comprise two O-demethylated derivatives and an N-oxidation product. Donepezil is metabolised by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. The rate of metabolism of donepezil is slow and does not appear to be saturable. These findings are consistent with the results from formal pharmacokinetic studies which showed that donepezil and/or its metabolites does not inhibit the metabolism of theophylline, warfarin, cimetidine, or digoxin in humans. Pharmacokinetic studies also demonstrated that the metabolism of donepezil is not affected by concurrent administration of digoxin or cimetidine (see Section 4.5 Interactions with other medicines and other forms of interactions).

Following administration of ^{14}C-labelled donepezil, plasma radioactivity, expressed as a percent of the administered dose, was present primarily as intact donepezil (53%) and as 6-O desmethyl donepezil (11%) which has been reported to inhibit AChE to the same extent as donepezil *in vitro* and was found in the plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and faeces, respectively, over a period of 10 days, while 28% remained unrecovered, with about 17% of the donepezil dose recovered in the urine as unchanged drug.

There is no evidence to suggest enterohepatic re-circulation of donepezil and/or any of its metabolites.

Plasma donepezil concentrations decline with a half life of approximately 70 hours.

Special Populations

Sex, race and smoking history have no clinically significant influence on plasma concentrations of donepezil.

Pharmacokinetic/dynamic Properties

Characteristics in Patients

As an inhibitor of AChE, donepezil augments cholinergic function in the central nervous system, thereby providing its therapeutic benefit. The enzyme AChE also occurs peripherally in red blood cells, therefore, measurement of AChE activity in erythrocyte membranes provides an index for donepezil pharmacodynamics. This surrogate marker has been evaluated in several human pharmacokinetic/pharmacodynamic trials and in controlled clinical trials.

The population plasma donepezil concentrations and red blood cell AChE inhibition measurements verified that patients in clinical trials experienced exposure to donepezil hydrochloride and its pharmacodynamic actions as predicted.

Results from therapeutic drug monitoring showed no apparent relationship between plasma concentration and adverse drug reactions.

Two double blind randomised trials showed statistically significant drug placebo differences for each of the two primary outcome measures (ADAS-cog and CIBIC plus). ADAS-cog examines cognitive performance - including memory, orientation, attention, reason, language and praxis. The CIBIC Plus is a global measure of change in patient functionality that is derived through evaluation of four major areas of functioning (general, cognition, behaviour and activities of daily living). The analyses of secondary efficacy variables (MMSE, CDR-SB) support the results of the primary efficacy analyses.

5.3 Preclinical safety data

Genotoxicity

Donepezil was not mutagenic in reverse mutation assays in bacteria or in the mouse lymphoma forward mutation assay *in vitro*. Donepezil did not induce unscheduled DNA synthesis in rat primary hepatocyte cultures following oral dosing of the animals. In the chromosome aberration test in cultures of Chinese hamster lung cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in-vivo* mouse micronucleus test.

Carcinogenicity

No evidence of carcinogenicity was found in long-term studies in mice and rats with dietary dosing of donepezil resulting in peak plasma concentrations of up to 17 times and 6–19 times, respectively, that in humans at the recommended clinical dose of 10 mg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, maize starch, microcrystalline cellulose, hyprolose and magnesium stearate. The film coating contains purified talc, macrogol 8000, hypromellose and titanium dioxide. Additionally, the 10 mg tablet contains iron oxide yellow as a colouring agent.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

ARICEPT film-coated, round tablets, containing either 5 mg or 10 mg donepezil hydrochloride, are packaged in PVC/AI blister packs of 28 tablets.

Not all presentations may be marketed.

6.6 Special precautions for disposal

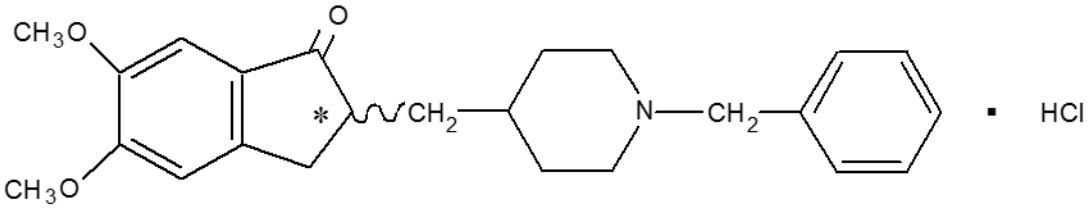
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Donepezil hydrochloride is a white crystalline powder and is 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.

Chemical structure

The structural formula of donepezil hydrochloride is shown below:



Chemical name: (RS)-1-benzyl-4-[5,6-dimethoxy-1-indanon)-2-yl] -methylpiperidine hydrochloride

Molecular formula: $C_{24}H_{29}NO_3HCl$

Molecular weight: 415.96

CAS number

120011-70-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (S4)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

30 March 1998

10. DATE OF REVISION

25 October 2024

Summary Table of Changes

Section changed	Summary of new information
2	Corrected section on excipients with known effects.
4.8	Addition of hypersexuality, pleurothotonus (Pisa syndrome) per TGA request.
6.1	Editorial update.
8	Updated sponsor addres.

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