

Once-a-day Aricept*

donepezil HCl 5 & 10 mg tablets

PHARMACOLOGIC CLASSIFICATION

Cholinesterase Inhibitor

ACTION AND CLINICAL PHARMACOLOGY

ARICEPT (donepezil hydrochloride) is a pyridine-based, reversible inhibitor of the enzyme acetylcholinesterase.

A consistent pathological change in Alzheimer's Disease is the degeneration of cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. The resulting hypofunction of these pathways is thought to account for some of the clinical manifestations of dementia. Donepezil is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine (ACh) through reversible inhibition of its hydrolysis by acetylcholinesterase (AChE). If this proposed mechanism of action is correct, donepezil's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact.

There is no evidence that donepezil alters the course of the underlying dementing process.

Clinical Pharmacokinetics and Metabolism

Absorption: Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations (C_{max}) approximately 3 to 4 hours after dose administration. Plasma concentrations and area under the curve (AUC) were found to rise in proportion to the dose administered within the 1- to 10 mg dose range studied. The terminal disposition half-life ($t_{1/2}$) is approximately 70 hours and the mean apparent plasma clearance (Cl/F) is 0.13L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold and steady state is reached within 15 days. The minimum, maximum and steady-state plasma concentrations (C) and pharmacodynamic effect (E, percent inhibition of erythrocyte membrane acetylcholinesterase in erythrocyte membranes) of donepezil hydrochloride in healthy adult male and female volunteers are given in Table 1.

Table 1. Plasma Concentrations and Pharmacodynamic Effect of Donepezil Hydrochloride at Steady-State (Mean \pm S.D.)

Dose (mg/day)	C_{min} (ng/mL)	C_{max} (ng/mL)	C_{ss}^1 (ng/mL)	E_{min} %	E_{max} %	E_{ss}^2 %
5	21.4 \pm 3.8	34.1 \pm 7.3	26.5 \pm 3.9	62.2 \pm 5.8	71.8 \pm 4.3	65.3 \pm 5.2
10	38.5 \pm 8.6	60.5 \pm 10.0	47.0 \pm 8.2	74.7 \pm 4.4	83.6 \pm 1.9	77.8 \pm 3.0

¹ C_{ss} : Plasma concentration at steady state

² E_{ss} : Inhibition of erythrocyte membrane acetylcholinesterase at steady state

The range of inhibition of erythrocyte membrane acetylcholinesterase noted in Alzheimer's Disease patients in controlled clinical trials was 40- to 80% and 60- to 90% for the 5 mg/day and 10 mg/day doses, respectively.

Pharmacokinetic parameters from healthy adult male and female volunteers participating in a multiple-dose study where single daily doses of 5 mg or 10 mg of donepezil hydrochloride were administered each evening are summarized in Table 2. Treatment duration was one month. However, volunteers randomized to the 10 mg/day dose group initially received 5 mg daily doses of donepezil for one week before receiving the 10 mg daily dose for the next three weeks in order to avoid acute cholinergic effects.

Table 2. Pharmacokinetic Parameters of Donepezil Hydrochloride at Steady-State (Mean \pm S.D.)

Dose (mg/day)	t_{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)	Cl _r /F (L/hr/kg)	V _d /F (L/kg)	$t_{1/2}$ (hr)
5	3.0 \pm 1.4	634.8 \pm 92.2	0.110 \pm 0.02	11.8 \pm 1.7	72.7 \pm 10.6
10	3.9 \pm 1.0	1127.8 \pm 195.9	0.110 \pm 0.02	11.6 \pm 1.9	73.5 \pm 11.8

t_{max} : Time to maximal plasma concentration

AUC₀₋₂₄: Area under the plasma concentration versus time curve from 0- to 24 hours

Cl_r/F: Mean apparent plasma clearance

V_d/F: Apparent volume of distribution

$t_{1/2}$: Elimination half-life

Neither food nor time of dose administration (i.e., morning versus evening dose) have an influence on the rate and extent of donepezil hydrochloride absorption.

The effect of achlorhydria on the absorption of donepezil hydrochloride is unknown.

Distribution: Donepezil hydrochloride is about 96% bound to human plasma proteins, mainly to albumins (~75%) and α_1 -acid glycoprotein (~21%) over the concentration range of 2- to 1000 ng/mL.

Metabolism/Excretion: Donepezil hydrochloride is extensively metabolized and is also excreted in the urine as parent drug. The rate of metabolism of donepezil hydrochloride is slow and does not appear to be saturable. There are four major metabolites - two of which are known to be active - and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. 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 unchanged donepezil hydrochloride (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 plasma at concentrations equal to about 20% of donepezil. Approximately 57% of the total administered radioactivity was recovered from the urine and 15% was recovered from the faeces (total recovery of 72%) over a period of 10 days. Approximately 28% of the labelled donepezil remained uncovered, with about 17% of the donepezil dose recovered in the urine as parent drug.

Age and Gender: No formal pharmacokinetic study was conducted to examine age and gender-related differences in the pharmacokinetic profile of donepezil. However, mean plasma donepezil concentrations measured during therapeutic drug monitoring of elderly male and female patients with Alzheimer's Disease are comparable to those observed in young healthy volunteers.

Renal: In a study of four patients with moderate-to-severe renal impairment (Cl_{cr} <22 mL/min/1.73 m²), the clearance of donepezil did not differ from that of four age and sex-matched healthy subjects.

Hepatic: In a study of 10 patients with stable alcoholic cirrhosis, the clearance of donepezil was decreased by 20% relative to 10 healthy age and sex-matched subjects.

Race: No specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of donepezil. However, retrospective pharmacokinetic analysis indicates that gender and race (Japanese and Caucasians) did not affect the clearance of donepezil.

Clinical Trial Data: Two randomized, double-blind, placebo-controlled, clinical trials, in patients with Alzheimer's Disease (diagnosed by DSM-III-R and NINCDS criteria, Mini-Mental State Examination \geq 10 and \leq 26 as well as a Clinical Dementia Rating of 1 or 2) provided efficacy data for donepezil in this

patient population. In these studies, the mean age of patients was 73 years with a range of 50 to 94 years. Approximately 64% of the patients were women and 38% were men. The racial distribution was as follows: white: 95%, black: 3% and other races: 2%.

In each study, the effectiveness of treatment with donepezil was evaluated using a dual outcome assessment strategy. The ability of donepezil to improve cognitive performance was assessed with the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a widely used and well validated multi-item instrument which samples cognitive domains affected by the disease.

The ability of donepezil to produce an overall clinical effect was assessed using the semi-structured CIBIC plus (Clinician's Interview Based Impression of Change that required the use of caregiver information). The CIBIC plus evaluates four major areas of functioning: general, cognition, behavior and activities of daily living.

The data shown below for the two primary outcome measures in donepezil clinical trials were obtained from the Intent-To-Treat population (ITT analysis, i.e., All patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete the study, their last observation while on treatment was carried forward and used at endpoint).

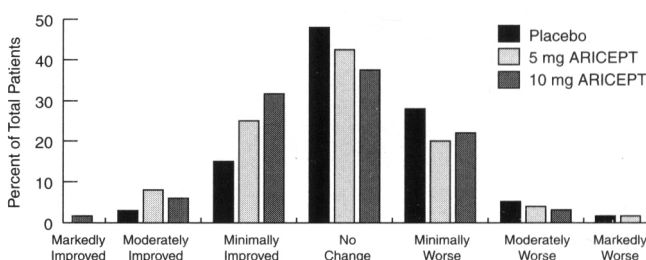
Fifteen-Week Study (12 weeks of treatment + 3-week placebo washout):

In this study, 468 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of donepezil for 12 weeks, followed by a 3-week placebo washout period. To reduce the likelihood of cholinergic effects, the 10 mg/day treatment group received 5 mg/day for the first week prior to receiving their first 10 mg daily dose.

Effects on ADAS-cog: Patients treated with donepezil showed significant improvements in ADAS-cog score from baseline, and when compared with placebo. The difference in mean ADAS-cog change scores for the donepezil-treated patients compared to the patients on placebo, for the intent-to-treat population, at week 12 were 2.44 \pm 0.43 and 3.07 \pm 0.43 units each, for the 5 mg/day and 10 mg/day donepezil treatment groups, respectively. These differences were statistically significant. The difference between active treatments was not statistically significant. Following a 3-week placebo washout period, the ADAS-cog scores for both donepezil treatment groups increased, indicating that discontinuation of donepezil resulted in a loss of its treatment effect. The duration of this placebo washout period was not sufficient to characterize the rate of loss of the treatment effect, but, the 30-week study (see below) demonstrated that treatment effects associated with the use of donepezil abate within 6 weeks of treatment discontinuation.

Effects on The CIBIC plus: The CIBIC plus showed significant improvement with donepezil treatment versus placebo. The differences in mean scores for donepezil-treated patients compared to those on placebo for the intent-to-treat population at Week 12 were 0.29 \pm 0.08 and 0.34 \pm 0.08 units for the 5 mg/day and 10 mg/day treatment groups, respectively. These differences from placebo were statistically significant. There was no significant difference between the two active treatments. Figure 1 is a histogram of the frequency distribution of CIBIC plus scores achieved at Week 12 by patients assigned to each of the three treatment groups.

Fig 1. FREQUENCY DISTRIBUTION OF CIBIC PLUS SCORES AT WEEK 12



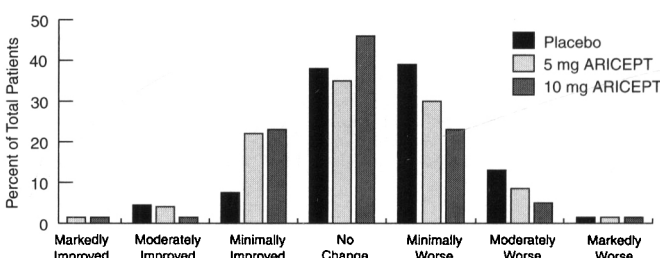
Thirty-Week Study (24 weeks of treatment + 6-week placebo washout):

In this study, 473 patients were randomized to receive single daily doses of placebo, 5 mg/day or 10 mg/day of donepezil for 24 weeks of double-blind active treatment followed by a 6-week single-blind placebo washout period. As in the 15-week study to avoid acute cholinergic effects, the 10 mg/day treatment group received 5 mg/day for the first week prior to receiving their first 10 mg daily dose.

Effects on The ADAS-cog: Patients treated with donepezil showed significant improvements in ADAS-cog score from baseline, and when compared with placebo. The mean differences in the ADAS-cog change scores for donepezil-treated patients compared to the patients on placebo for the intent-to-treat population at Week 24 were 2.49 \pm 0.51 and 2.88 \pm 0.51 units for the 5 mg/day and 10 mg/day treatments, respectively. These differences were statistically significant. The difference between the two active treatments was not statistically significant. Over the 24-week treatment period, 80% (5 mg) and 81% (10 mg) of donepezil-treated patients versus 58% placebo-treated patients showed no evidence of deterioration or an improvement. A 4-point improvement in ADAS-cog was observed in 38% (5 mg) and 54% (10 mg) of donepezil-treated patients versus 27% for placebo. A 7-point improvement was observed in 15% (5 mg) and 25% (10 mg) of donepezil-treated patients versus 8% for placebo. 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 donepezil abate over 6 weeks following discontinuation of treatment and therefore do not represent a change in the underlying disease. There was no evidence of a rebound effect 6 weeks after abrupt discontinuation of therapy. This is in line with the pharmacokinetics of donepezil (i.e., ~70 hour half-life) which preclude an abrupt reduction in drug plasma levels.

Effects on The CIBIC plus: After 24 weeks of treatment, the mean drug-placebo differences were 0.36 \pm 0.09 and 0.44 \pm 0.07 units for 5 mg/day and 10 mg/day of donepezil, respectively. These differences were statistically significant. There was no statistically significant difference between the two active treatments. Figure 2 is a histogram of the frequency distribution of CIBIC plus scores achieved at Week 24 by patients assigned to each of the three treatment groups.

Fig 2. FREQUENCY DISTRIBUTION OF CIBIC PLUS SCORES AT WEEK 24



Data from these controlled clinical trials showed that the beneficial symptomatic effects of ARICEPT versus placebo were more consistently apparent after 12 weeks of continuous treatment. Once treatment is discontinued, the effects of ARICEPT were shown to abate within 6 weeks of treatment discontinuation.

INDICATIONS AND CLINICAL USE

ARICEPT (donepezil hydrochloride) is indicated for the symptomatic treatment of patients with mild-to-moderate dementia of the Alzheimer's type. ARICEPT has not been studied in controlled clinical trials for longer than 6 months.

ARICEPT tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's Disease.

CONTRAINDICATIONS

ARICEPT (donepezil hydrochloride) is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives.

WARNINGS

Anaesthesia: ARICEPT (donepezil hydrochloride), as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anaesthesia.

Neurological Conditions: Seizures: Some cases of seizures have been reported with the use of ARICEPT in clinical trials and from spontaneous Adverse Reaction reporting. Cholinomimetics can cause a reduction of seizure threshold, increasing the risk of seizures. However, seizure activity may also be a manifestation of Alzheimer's Disease. The risk/benefit of ARICEPT treatment for patients with a history of seizure disorder must therefore be carefully evaluated.

ARICEPT has not been studied in patients with moderately severe or severe Alzheimer's Disease, non-Alzheimer dementias or individuals with Parkinsonian features. The efficacy and safety of ARICEPT in these patient populations is unknown.

Pulmonary Conditions: Because of their cholinomimetic action, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. ARICEPT has not been studied in patients under treatment for these conditions and should therefore be used with particular caution in such patients.

Cardiovascular: 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. In clinical trials, most patients with significant cardiovascular conditions were excluded, except for patients with: controlled hypertension (DBP < 95 mmHg), right bundle branch blockage, and pacemakers. Therefore, caution should be taken in treating patients with active coronary artery disease and congestive heart failure. Syncopal episodes have been reported in association with the use of ARICEPT. It is recommended that ARICEPT should not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes.

Gastrointestinal: Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent non-steroidal anti-inflammatory drugs (NSAIDs) including high doses of acetylsalicylic acid (ASA), should be monitored closely for symptoms of active or occult gastrointestinal bleeding. Clinical studies of ARICEPT have shown no increase, relative to placebo in the incidence of either peptic ulcer disease or gastrointestinal bleeding. (See ADVERSE REACTIONS Section.)

ARICEPT, as a predictable consequence of its pharmacological properties, has been shown to produce, in controlled clinical trials in patients with Alzheimer's Disease, diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg dose than with the 5 mg dose. In most cases, these effects have usually been mild and transient, sometimes lasting one -to- three weeks and have resolved during continued use of ARICEPT. (See ADVERSE REACTIONS Section.) A treatment with the 5 mg/day dose for over 6 weeks prior to initiating treatment with the 10 mg/day dose is associated with a lower incidence of gastrointestinal intolerance.

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

PRECAUTIONS

Concomitant Use with Other Drugs:

Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Use with Other Psychoactive Drugs: Few patients in controlled clinical trials received neuroleptics, antidepressants or anticonvulsants; there is thus limited information concerning the interaction of ARICEPT with these drugs.

Use in Patients ≥ 85 Years Old: In controlled clinical studies with 5 and 10 mg of ARICEPT, 536 patients were between the ages of 65 to 84, and 37 patients were aged 85 years or older. In Alzheimer's Disease patients, nausea, diarrhea, vomiting, insomnia, fatigue and anorexia increased with dose and age and the incidence appeared to be greater in female patients. Since cholinesterase inhibitors as well as Alzheimer's Disease can be associated with significant weight loss, caution is advised regarding the use of ARICEPT in low body-weight elderly patients, especially in those ≥ 85 years old.

Use in Elderly Patients with Comorbid Disease: There is limited safety information for ARICEPT in patients with mild-to-moderate Alzheimer's Disease and significant comorbidity. The use of ARICEPT in Alzheimer's Disease patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Caution is advised regarding the use of ARICEPT doses above 5 mg in this patient population.

Renally and Hepatically Impaired: There is limited information regarding the pharmacokinetics of ARICEPT in renally and hepatically impaired Alzheimer's Disease patients (see Clinical Pharmacokinetics and Metabolism section). Close monitoring for adverse effects in Alzheimer's Disease patients with renal or hepatic disease being treated with ARICEPT is therefore recommended.

Drug-Drug Interactions:

Pharmacokinetic studies, limited to short-term, single-dose studies in young subjects evaluated the potential of ARICEPT for interaction with theophylline, cimetidine, warfarin and digoxin administration. No significant effects on the pharmacokinetics of these drugs were observed. Similar studies in elderly patients were not done.

Drugs Highly Bound to Plasma Proteins: Drug displacement studies have been performed *in vitro* between donepezil, a highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. Donepezil at concentrations of 0.3 - 10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL) and warfarin (3 µg/mL) to human albumin. Similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin.

Effect of ARICEPT on The Metabolism of Other Drugs: No *in vivo* clinical trials have been conducted to investigate the effect of ARICEPT on the clearance of drugs metabolized 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 interferences.

It is not known whether ARICEPT has any potential for enzyme induction.

Effect of Other Drugs on The Metabolism of 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. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin and phenobarbital) could increase the rate of elimination of ARICEPT.

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

Use in Pregnancy and Nursing Mothers: The safety of ARICEPT during pregnancy and lactation has not been established and therefore, it should not be used in women of childbearing potential or in nursing mothers unless, in the opinion of the physician, the potential benefits to the patient outweigh the possible hazards to the fetus or the infant.

Teratology studies conducted in pregnant rats at doses of up to 16 mg/kg/day and in pregnant rabbits at doses of up to 10 mg/kg/day did not disclose any evidence for a teratogenic potential of ARICEPT.

Pediatric Use: There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT in any illness occurring in children. Therefore, ARICEPT is not recommended for use in children.

ADVERSE REACTIONS

A total of 747 patients with mild-to-moderate Alzheimer's Disease were treated in controlled clinical studies with ARICEPT (donepezil hydrochloride). Of these patients, 613 (82%) completed the studies. The mean duration of treatment for all ARICEPT groups was 132 days (range 1-356 days).

Adverse Events Leading to Discontinuation:

The rates of discontinuation from controlled clinical trials of ARICEPT due to adverse events for the ARICEPT 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received the 10 mg/day dose after only a 1-week initial treatment with 5 mg/day ARICEPT was higher at 13%.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group

Dose Group	Placebo	5 mg/day ARICEPT	10 mg/day ARICEPT
Number of Patients Randomized	355	350	315
Events/% Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

Most Frequent Adverse Clinical Events Seen in Association with The Use of ARICEPT:

The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT's cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT treatment without the need for dose modification.

There is evidence to suggest that the frequency of these common adverse events may be affected by the duration of treatment with an initial 5 mg daily dose prior to increasing the dose to 10 mg/day. An open-label study was conducted with 269 patients who received placebo in the 15 and 30-week studies. These patients received a 5 mg/day dose for 6 weeks prior to initiating treatment with 10 mg/day. The rates of common adverse events were lower than those seen in controlled clinical trial patients who received 10 mg/day after only a one-week initial treatment period with a 5 mg daily dose, and were comparable to the rates noted in patients treated only with 5 mg/day.

See Table 2 for a comparison of the most common adverse events following one and six-week initial treatment periods with 5 mg/day ARICEPT.

Table 2. Comparison of Rates of Adverse Events in Patients Treated with 10 mg/day after 1 and 6 Weeks of Initial Treatment with 5 mg/day

Adverse Event	No Initial Treatment		One-Week Initial Treatment with 5 mg/day	Six-Week Initial Treatment with 5 mg/day
	Placebo (n = 315)	5 mg/day (n = 311)	10 mg/day (n = 315)	10 mg/day (n = 269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle Cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Adverse Events Reported in Controlled Trials:

The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment-emergent signs and symptoms (TESS) that were reported in at least 2% of patients from placebo-controlled clinical trials who received ARICEPT and for which the rate of occurrence was greater for ARICEPT than placebo-assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

Table 3. Adverse Events Reported In Controlled Clinical Trials In At Least 2% of Patients Receiving ARICEPT and at a Higher Frequency than Placebo-Treated Patients

Body System/ Adverse Events	Body System/ Adverse Events		Body System/ Adverse Events	
	Placebo n = 355	ARICEPT n = 747	Placebo n = 355	ARICEPT n = 747
Percent of Patients with any Adverse Event	72	74		
Body as a Whole				
Headache	9	10		
Pain, Various Locations	8	9		
Accident	6	7		
Fatigue	3	5		
Cardiovascular System				
Syncope	1	2		
Digestive System				
Nausea	6	11		
Diarrhea	5	10		
Vomiting	3	5		
Anorexia	2	4		
Hemic and Lymphatic Systems				
Echymosis	3	4		

Other Adverse Events Observed During Clinical Trials:

ARICEPT has been administered to over 1700 individuals for various lengths of time during clinical trials worldwide. Approximately 1200 patients have been treated for at least 3 months, and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 115 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days.

Treatment-emergent signs and symptoms that occurred during three controlled clinical trials and two open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the studies were integrated and the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT. All adverse events occurring at least twice are included. Adverse events already listed in Tables 2 and 3 are not repeated here (i.e., events occurring at an incidence >2%). Also excluded are COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed as occurring in ≥1% and <2% of patients (i.e., in 1/100 to 2/100 patients: *frequent*) or in <1% of patients (i.e., in 1/100 to 1/1000 patients: *infrequent*). These adverse events are not necessarily related to ARICEPT treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Adverse Events Occurring in ≥1% and <2% or <1% of Patients Receiving ARICEPT:

Body as a Whole: (≥1% and <2%) influenza, chest pain, toothache; (<1%) fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, head pressure, listlessness.

Cardiovascular System: (≥1% and <2%) hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; (<1%) angina pectoris, postural hypotension, myocardial infarction, premature ventricular contraction, arrhythmia, AV Block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thromboses.

Digestive System: (≥1% and <2%) faecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; (<1%) eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, haemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer.

Endocrine System: (<1%) diabetes mellitus, goiter.

Hemic & Lymphatic System: (<1%) anaemia, thrombocytopenia, thrombocytopenia, eosinophilia, erythrocytopenia.

Metabolic and Nutritional Disorders: (≥1% and <2%) dehydration; (<1%) gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase.

Musculoskeletal System: (≥1% and <2%) bone fracture; (<1%) muscle weakness, muscle fasciculation.

Nervous System: (≥1% and <2%) delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, libido increased, restlessness, abnormal crying, nervousness, aphasia; (<1%) cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing, seizures.

Respiratory System: (≥1% and <2%) dyspnea, sore throat, bronchitis; (<1%) epistaxis, postnasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring.

Skin and Appendages: (≥1% and <2%) abrasion, pruritus, diaphoresis, urticaria; (<1%) dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer.

Special Senses: (≥1% and <2%) cataract, eye irritation, blurred vision; (<1%) dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes.

Urogenital System: (≥1% and <2%) urinary incontinence, nocturia; (<1%) dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

Treatment: The elimination half-life of ARICEPT at recommended doses is approximately 70 hours, thus, in the case of overdose, it is anticipated that prolonged treatment and monitoring of adverse and toxic reactions will be necessary. As in any case of overdose, general supportive measures should be utilized.

Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT (donepezil hydrochloride) overdose. Intravenous atropine sulfate 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 ARICEPT and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

Dose-related signs of toxicity observed in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, fasciculation, and lower body surface temperature.

DOSEAGE AND ADMINISTRATION

ARICEPT (donepezil hydrochloride) tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's Disease.

The recommended initial dose of ARICEPT is 5 mg taken once daily. Therapy with the 5 mg dose should be maintained for 4-6 weeks before considering a dose increase, in order to avoid or decrease the incidence of the most common adverse reactions to the drug (see **ADVERSE REACTIONS** section) and to allow plasma levels to reach steady state.

For those patients who do not respond adequately to the 5 mg daily dose after 4 -to- 6 weeks of treatment, the 10 mg daily dose may then be considered.

The maximum recommended dose is 10 mg taken once daily.

Following initiation of therapy or any dosage increase, patients should be closely monitored for adverse effects. Adverse events are more common in individuals of low body weight, in patients ≥ 85 years old and in females. It is recommended that ARICEPT be used with caution in elderly women of low body weight and that the dose should not exceed 5 mg/day.

ARICEPT should be taken once daily in the evening, before retiring. It may be taken with or without food.

In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

Composition:

Each 5 and 10 mg, film-coated tablet contains 5.00 and 10.00 mg of donepezil HCl respectively, equivalent to 4.56 and 9.12 mg of donepezil free base. Inactive ingredients are lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropylcellulose, and magnesium stearate. The film coating contains talc, polyethylene glycol, hydroxypropyl methylcellulose and titanium dioxide. Additionally, the 10 mg tablet contains iron oxide as a colouring agent.

Stability and Storage Recommendations:

Store at controlled room temperature, 15°C to 30°C and away from moisture.

AVAILABILITY OF DOSAGE FORMS

ARICEPT is supplied as film-coated tablets containing 5 mg (white tablets) or 10 mg (yellow tablets) of donepezil hydrochloride. The name ARICEPT and the strength are embossed on each tablet.

ARICEPT is available in high density polyethylene (HDPE) bottles of 30.

REFERENCES:

1. Ashford JW. Diagnosis of Alzheimer's disease. *Psychiatric Annals*, 1996 May 1;26(5):262-268.
2. ARICEPT Product Monograph. Pfizer Canada Inc.

Full Product Monograph available upon request.



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