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Once-a-day Aricept*

donepezil HCl 5 & 10 mg tablets

PHARMACOLOGIC CLASSIFICATION: Cholinesterase Inhibitor. **ACTION AND CLINICAL PHARMACOLOGY:** **ARICEPT** (donepezil hydrochloride) is a piperidine-based, reversible inhibitor of the enzyme acetylcholinesterase (AChE). 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 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. **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. Efficacy of **ARICEPT** in patients with mild-to-moderate Alzheimer's disease was established in two 24-week and one 54-week placebo-controlled trials. **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:** ***Anesthesia:*** **ARICEPT** (donepezil hydrochloride), as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. ***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 non-Alzheimer dementias or individuals with Parkinsonian features. The efficacy and safety of **ARICEPT** in these patients are 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 serious cardiovascular conditions were excluded. Patients such as those with controlled hypertension (DBP<85 mmHg), right bundle branch blockage and pacemakers were included. 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 nonsteroidal anti-inflammatory drugs (NSAIDs) including high doses of acetylsalicylic acid (ASA), should be monitored 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 1 to 3 weeks and have resolved during continued use of **ARICEPT** (See **ADVERSE REACTIONS** section). Treatment with the 5 mg/d dose for 4-6 weeks prior to increasing the dose to 10 mg/d 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. 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:*** In vitro studies show a low rate of donepezil binding to CYP 3A4 and CYP 2D6 isoenzymes (mean Ki about 50-130 µM), which, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interferences. In a pharmacokinetic study involving 18 healthy volunteers, the administration of **ARICEPT** at a dose of 5 mg/d for 7 days had no clinically significant effect on the pharmacokinetics of ketoconazole. No other 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). 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 CYP 450, 3A4 and 2D6, respectively, inhibit donepezil metabolism in vitro. In a pharmacokinetic study, 18 healthy volunteers received 5 mg/d **ARICEPT** together with 200 mg/d ketoconazole for 7 days. In these volunteers, mean donepezil plasma concentrations were increased by about 30-36%. 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 Mother:*** 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/d and in pregnant rabbits at doses of up to 10 mg/kg/d 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/d treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received the 10 mg/d dose after only a 1-week initial treatment with 5 mg/d **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/d ARICEPT	10 mg/d 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/d and twice the placebo rate, are largely predicted by **ARICEPT**'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, 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/d. 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/d dose for 6 weeks prior to initiating treatment with 10 mg/d. The rates of common adverse events were lower than those seen in controlled clinical trial patients who received 10 mg/d after only a 1-week initial treatment period with a 5 mg daily dose, and were comparable to the rates noted in patients treated only with 5 mg/d. See Table 2 for a comparison of the most common adverse events following 1- and 6-week initial treatment periods with 5 mg/d **ARICEPT**.

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

	No Initial Treatment		1-Week Initial Treatment with 5 mg/d	6-Week Initial Treatment with 5 mg/d
Adverse Event	**Placebo (n = 315)**	**5 mg/d (n = 311)**	**10 mg/d (n = 315)**	**10 mg/d (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 behaviour 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	Placebo n = 355	ARICEPT n = 747	Body System/ Adverse Events	Placebo n = 355	ARICEPT n = 747
Percent of Patients with any Adverse Event	72	74	**Metabolic and Nutritional**		
Body as a Whole			Weight Decrease	1	3
Headache	9	10	**Musculoskeletal System**		
Pain, various locations	8	9	Muscle Cramps	2	6
Accident	6	7	Arthritis	1	2
Fatigue	3	5	**Nervous System**		
Cardiovascular System			Insomnia	6	9
Syncope	1	2	Dizziness	6	8
Digestive System			Depression	<1	3
Nausea	6	11	Abnormal Dreams	0	3
Diarrhea	5	10	Somnolence	<1	2
Vomiting	3	5	**Urogenital**		
Anorexia	2	4	Frequent Urination	1	2
Hemic and Lymphatic Systems					
Ecchymosis	3	4			

Other Adverse Events Observed During Clinical Trials: During the pre-marketing phase, **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/d, 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 3 placebo-controlled clinical trials and 2 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%) fecal 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, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. ***Endocrine System:*** (<1%) diabetes mellitus, goiter. ***Hemic & Lymphatic System:*** (<1%) anemia, thrombocythemia, 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. ***Long-Term Safety:*** Patients were exposed to **ARICEPT** in 2 open-label extension studies (n = 885) of over 2 years. In 1 of the studies, 763 patients who previously completed 1 of 2 placebo-controlled studies of 15 or 30 weeks duration continued to receive **ARICEPT** and were evaluated for safety and neuropsychological evaluations for up to 152 weeks; the safety profile of **ARICEPT** in this extension study remained consistent with that observed in placebo-controlled trials. Following 1 and 2 years of treatment, 76% (n = 580) and 49% (n = 374) of these patients, respectively, were still receiving therapy (cumulative Weeks 48 and 108). ***Post-marketing Reports:*** Voluntary reports of adverse events temporally associated with **ARICEPT** that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash. **DOSAGE 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. ***Adults:*** 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. Based on clinical judgement, the 10 mg daily dose may be considered following 4-6 weeks of treatment at 5 mg/d. 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. **ARICEPT** should be taken once-daily in the morning or evening. It may be taken with or without food. ***Special Populations:*** 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 these patient populations. In elderly women of low body weight, the dose should not exceed 5 mg/d. In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision. **AVAILABILITY OF DOSAGE FORMS:** **ARICEPT** (donepezil hydrochloride) 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 and 100 tablets and in blister strips boxed as 7, 14 and 28 tablets (combination of 2 strips of 14 tablets).

References

1. IMS Health; IMS Midas, June 2003. **2.** Winblad B et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* 2001;57(3):489-495. **3.** Mohs RC et al. A 1-year placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* 2001;57(3):481-488. **4.** Gauthier S et al. Functional, cognitive and behavioral effects of donepezil in patients with moderate Alzheimer's disease. *Curr Med Res Opin* 2002;18(6):347-354. **5.** Aricept* Product Monograph. Pfizer Canada Inc., July 2003.

Product Monograph available on request.

Pfizer NEUROSCIENCES

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