

# THE CLOCK DRAW TEST

## About the test

Drawing a clock by hand is one of several useful screening tools. It can help a doctor tell the difference between normal aging and dementias such as Alzheimer's. It requires a person to use many different skills and abilities.

## Taking the test

Draw the face of a clock and put the numbers in the correct positions. Then draw the hands to indicate 8:20.

Draw the clock below.



See the next page to learn about scoring the Clock Draw Test.

ARICEPT<sup>®</sup> (donepezil HCl tablets) is indicated for the treatment of mild, moderate, and severe dementia of the Alzheimer's type.

### Important Safety Information

ARICEPT is well tolerated but may not be for everyone. People at risk for stomach ulcers or who take certain other medicines should tell their doctors because serious stomach problems, such as bleeding, may get worse.

Some people who take ARICEPT may experience fainting.

Some people may have nausea, vomiting, diarrhea, bruising, or not sleep well. Some people may have muscle cramps or loss of appetite or may feel tired. In studies these were usually mild and temporary.

Please see full prescribing information or visit [aricept.com](http://aricept.com).

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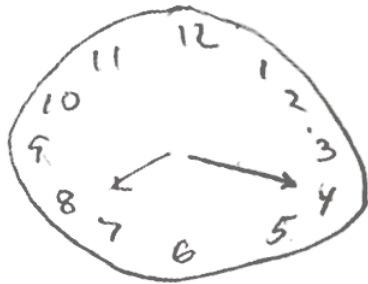
# THE CLOCK DRAW TEST

## Scoring

To score, assign the following points for each part of the drawing:

- 1 point for a closed circle
- 1 point for properly placed numbers
- 1 point for including all twelve numbers
- 1 point for properly placed hands

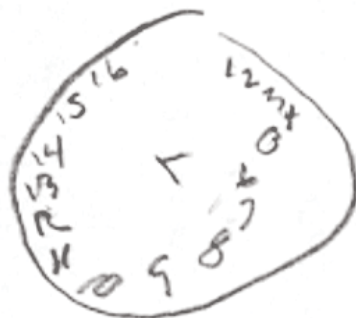
These clocks were drawn by patients asked to show 8:20.



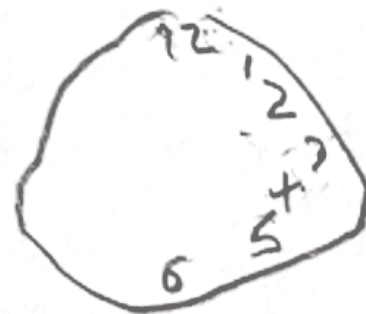
.....  
Clock score: 4



.....  
Clock score: 3



.....  
Clock score: 1



.....  
Clock score: 0



foot with ARICEPT® ODT is expected to be minimal. ARICEPT® ODT can be taken without regard to meals. The elimination half life of donepezil is about 70 hours and the mean apparent plasma clearance (Cl/F) is 0.13 L/hr/kg. Following multiple dose administration, donepezil accumulates in plasma by 4-7 fold and steady state is reached within 15 days. The steady state volume of distribution is 12 L/kg. Donepezil is approximately 96% bound to human plasma proteins, mainly to albumins (about 75%) and alpha<sub>1</sub>-acid glycoprotein (about 21%) over the concentration range of 2-1000 ng/mL.

Donepezil is both inhaled and extensively metabolized 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. Donepezil is metabolized by CYP 450 isozymes 2D6 and 3A4 and undergoes glucuronidation. Following administration of <sup>14</sup>C-labeled 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 plasma at concentrations equal to about 20% of donepezil. Approximately 57% and 15% of the total radioactivity was recovered in urine and feces, 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.

**Special Populations:** In a study of 10 patients with stable alcoholic cirrhosis, the clearance of ARICEPT® was decreased by 20% relative to 10 healthy age and sex matched subjects.

**Renal Disease:** In a study of 11 patients with moderate to severe renal impairment (ClCr <18 mL/min/1.73 m<sup>2</sup>), the clearance of ARICEPT® did not differ from 11 age and sex matched healthy subjects.

**Age:** No formal pharmacokinetic study was conducted to examine age related differences in the pharmacokinetics of ARICEPT®. However, mean plasma ARICEPT® concentrations measured during therapeutic drug monitoring of elderly patients with Alzheimer's Disease are comparable to those observed in young healthy volunteers.

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

**Drug-Drug 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 furosemide, digoxin, and warfarin. ARICEPT® 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 ARICEPT® 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 investigated 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 Ki 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, dimetidine, warfarin, digoxin and ketoconazole. No effects of ARICEPT® on the pharmacokinetics of these drugs were observed.

**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 quinidine is not known. In a 7-day crossover study in 18 healthy volunteers, ketoconazole (200 mg q.d.) increased mean donepezil (5 mg q.d.) concentrations (AUC<sub>0-24</sub> and C<sub>max</sub>) by 36%. The clinical relevance of this increase in concentration is unknown. Inducers of CYP 2D6 and CYP 3A4 (e.g. phenytoin, carbamazepine, dexamethasone, rifampin, 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.

**INDICATIONS AND USAGE**

ARICEPT® is indicated for the treatment of dementia of the Alzheimer's type. Efficacy has been demonstrated in patients with mild to moderate Alzheimer's Disease, as well as in patients with severe Alzheimer's Disease.

**CONTRAINDICATIONS**

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

**WARNINGS**

**Anesthetic:** ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

**Cardiovascular Conditions:** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart block, in patients both with and without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of ARICEPT®.

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

ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®.

**Genitourinary:** Although not observed in clinical trials of ARICEPT®, cholinesterase inhibitors may cause bladder outflow obstruction.

**Neurological Conditions:** Seizures. Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease.

**Pulmonary Conditions:** Because of their cholinergic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease.

**PRECAUTIONS**

**Drug-Drug Interactions** (see Clinical Pharmacology: Clinical Pharmacokinetics: Drug-drug Interactions)

Effect of ARICEPT® on the Metabolism of Other Drugs: No *in vivo* clinical trials have investigated 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 Ki about 50-130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference.

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

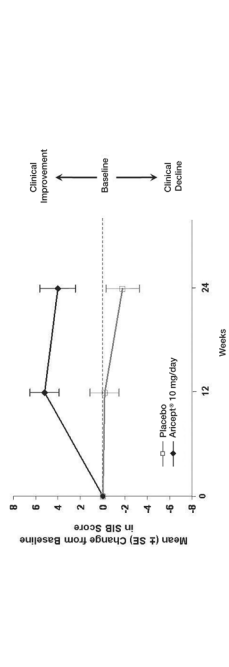


Figure 7 illustrates the cumulative percentages of patients from each of the two treatment groups who attained the measure of improvement in SIB score shown on the X-axis. While patients assigned both to ARICEPT® and to placebo have a wide range of responses, the curves show that the ARICEPT® group is more likely to show a greater improvement in cognitive performance.

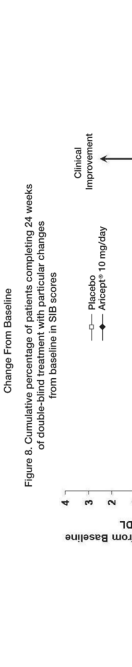
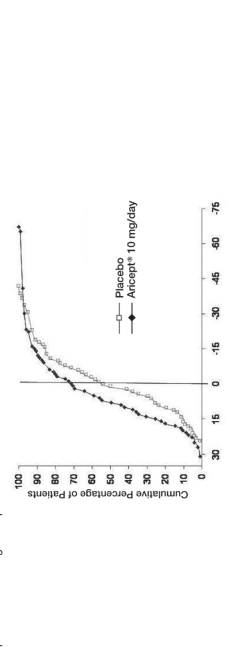


Figure 9 illustrates the time course for the change from baseline in ADCS-ADL-severe scores for patients in the two treatment groups over the 24 weeks of the study. After 24 weeks of treatment, the mean difference in the ADCS-ADL-severe change scores for ARICEPT® treated patients compared to patients on placebo was 1.8 units. ARICEPT® treatment was statistically significantly superior to placebo.

Figure 10 shows the cumulative percentages of patients from each treatment group with specified changes from baseline ADCS-ADL-severe scores. While both patients assigned to ARICEPT® and placebo have a wide range of responses, the curves demonstrate that the ARICEPT® group is more likely to show a smaller decline or an improvement.

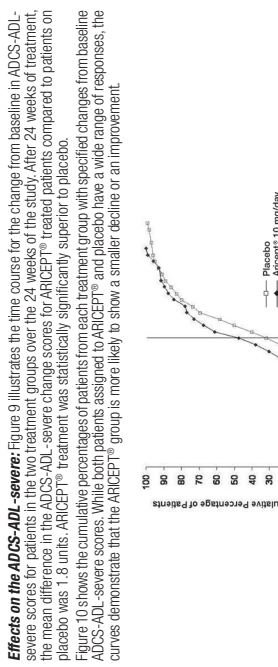


Figure 10 illustrates the time course for the change from baseline in ADCS-ADL-severe scores for patients in the two treatment groups over the 24 weeks of the study. After 24 weeks of treatment, the mean difference in the ADCS-ADL-severe change scores for ARICEPT® treated patients compared to patients on placebo was 1.8 units. ARICEPT® treatment was statistically significantly superior to placebo.

Figure 10 shows the cumulative percentages of patients from each treatment group with specified changes from baseline ADCS-ADL-severe scores. While both patients assigned to ARICEPT® and placebo have a wide range of responses, the curves demonstrate that the ARICEPT® group is more likely to show a smaller decline or an improvement.

**Japanese 24-Week Study**

In a study of 24 weeks duration, conducted in Japan, 325 patients with severe Alzheimer's Disease were randomized to doses of 5 mg/day or 10 mg/day of donepezil, administered once daily, or placebo. Patients randomized to treatment with donepezil were to achieve their assigned doses by titration, beginning at 3 mg/day, and extending over a maximum of 6 weeks. 248 patients completed the study with similar proportions of patients completing the study in each treatment group. The primary efficacy measures for this study were the SIB and CBIC plus.

At 24 weeks of treatment, statistically significant treatment differences were observed between the 10 mg/day dose of donepezil and placebo on both the SIB and CBIC plus. The 5 mg/day dose of donepezil showed a statistically significant superiority to placebo on the SIB, but not on the CBIC plus.

**Clinical Pharmacokinetics**

ARICEPT® ODT is bioequivalent to ARICEPT® Tablets. Donepezil is well absorbed with a relative oral bioavailability of 100% and reaches peak plasma concentrations in 3 to 4 hours. Pharmacokinetics are linear over a dose range of 1-10 mg given once daily. Neither food nor time of administration (morning vs. evening doses) influences the rate or extent of absorption of ARICEPT® Tablets. A food effect study has not been conducted with ARICEPT® ODT; however, the effect of

concurrent administration of digoxin or cimetidine.

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

**Use with Cholinergics 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.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

No evidence of a carcinogenic potential was obtained in an 88-week carcinogenicity study of donepezil hydrochloride conducted in CD-1 mice at doses up to 180 mg/kg/day (approximately 90 times the maximum recommended human dose) or in a 104-week carcinogenicity study in Sprague-Dawley rats at doses up to 30 mg/kg/day (approximately 30 times the maximum recommended human dose on a mg/m<sup>2</sup> basis).

Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria, or in a mouse lymphoma forward mutation assay *in vitro*. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test and was not genotoxic in an *in vivo* unscheduled DNA synthesis assay in rats.

Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m<sup>2</sup> basis).

**Pregnancy Category C:** Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m<sup>2</sup> basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m<sup>2</sup> basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m<sup>2</sup> basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers**

It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers.

**Pediatric Use**

There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children.

**Geriatric Use**

Alzheimer's disease is a disorder occurring primarily in individuals over 55 years of age. The mean age of patients enrolled in the clinical studies with ARICEPT® was 75. The efficacy of these patients were between 65 and 84 years old and 49% of the patients were at or above the age of 75. The efficacy and safety data presented in the clinical trials section were obtained from these patients. There were no clinically significant differences in most adverse events reported by patient groups ≥65 years old and <65 years old.

**ADVERSE REACTIONS**

**Mild to Moderate Alzheimer's Disease**

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 7-day escalators from 5 mg/day to 10 mg/day 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.

Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®
Patients Randomized	355	350	315
Event/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 cholinergic 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 rate of titration. An open-label study was conducted with 289 patients who received placebo in the 15 and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day.

See Table 2 for a comparison of the most common adverse events following one and six week titration regimens.

Adverse Event	No titration		One week titration		Six week titration	
	Placebo (n=315)	5 mg/day (n=311)	10 mg/day (n=315)	10 mg/day (n=269)	10 mg/day (n=269)	10 mg/day (n=269)
Nausea	6%	5%	19%	6%	9%	6%
Diarrhea	5%	8%	15%	9%	9%	6%
Insomnia	6%	6%	14%	6%	3%	3%
Fatigue	3%	3%	8%	8%	5%	5%
Vomiting	3%	3%	8%	8%	3%	3%
Muscle cramps	2%	6%	8%	8%	3%	3%
Anorexia	2%	3%	7%	7%	3%	3%

**Adverse Events Reported in Controlled Trials**

The events listed 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 in placebo or ARICEPT® treatment may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® 3 or 4

and for which the rate of occurrence was greater for ARICEPT<sup>®</sup> assigned 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 Mild to Moderate Alzheimer's Disease in at Least 2% of Patients Receiving ARICEPT<sup>®</sup> and at a Higher Frequency than Placebo-treated Patients**

Body System/Adverse Event	Placebo (n=355)	ARICEPT <sup>®</sup> (n=747)
<b>Percentage of Patients with any Adverse Event</b>	<b>72</b>	<b>74</b>
<b>Body as a Whole</b>		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
<b>Cardiovascular System</b>		
Syncope	1	2
<b>Digestive System</b>		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
<b>Hemic and Lymphatic System</b>		
Echymosis	3	4
<b>Metabolic and Nutritional Systems</b>		
Weight Decrease	1	3
<b>Musculoskeletal System</b>		
Muscle Cramps	2	6
Arthritis	1	2
<b>Nervous System</b>		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal Dreams	0	3
Somnolence	<1	2
<b>Urogenital System</b>		
Frequent Urination	1	2

**Other Adverse Events Observed During Clinical Trials**  
ARICEPT<sup>®</sup> has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these 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 116 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 controlled clinical trials and two open-label trials in the United States 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 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<sup>®</sup>. All adverse events occurring at least twice are included, except for those already listed in Tables 2 or 3. COSTART terms too general to be informative, or events less likely to be drug caused, are classified by body system and listed using the following definitions:  
**Frequent adverse events**—those occurring in at least 17/100 patients; **infrequent adverse events**—those occurring in 1/100 to 17/100 patients. These adverse events are not necessarily related to ARICEPT<sup>®</sup> treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States.

**Body as a Whole:** *Frequent:* fever, edema, face, periorbital edema, hemic facial abscess, cellulitis, chills, generalized coldness, head fullness, listlessness.  
**Cardiovascular System:** *Frequent:* hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; *Infrequent:* angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, aortic, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis.

**Digestive System:** *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* dry mouth, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, liver sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminase, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer.

**Endocrine System:** *Infrequent:* diabetes mellitus, goiter.

**Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocytopenia, eosinophilia, erythrocytopenia, creatine kinase, hypoglycemia, weight increase, increased lactate dehydrogenase.

**Musculoskeletal System:** *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation, nervousness.  
**Nervous System:** *Frequent:* delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypokinesia, neuroleptic malignant syndrome (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nycturia, pacing.

**Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, post nasal drip, pneumonia, hyperinflation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, stridor.  
**Skin and Appendages:** *Frequent:* pruritus, diaphoresis, urticaria; *Infrequent:* dermatitis, arthralgia, skin discoloration, hyperkeratosis, alopecia, tinea, contact dermatitis, herpes zoster, insect bite, sunburn, skin striae, night sweats, skin ulcer.

**Special Senses:** *Frequent:* catarract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, linitis, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes.

**Urogenital System:** *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, polydipsia, inability to empty bladder, breast fibroadenoma, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis.

**Severe Alzheimer's Disease**

**Adverse Events Leading to Discontinuation**  
The rates of discontinuation from controlled clinical trials of ARICEPT<sup>®</sup> due to adverse events for the ARICEPT<sup>®</sup> patients were approximately 12% compared to 7% for placebo patients.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of ARICEPT<sup>®</sup> patients and at twice the incidence seen in placebo patients, were anorexia (2% vs 1% placebo), nausea (2% vs <1% placebo), diarrhea (2% vs 0% placebo) and urinary tract infection (2% vs 1% placebo).

**Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT<sup>®</sup>**  
The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving ARICEPT<sup>®</sup> and twice the placebo rate, are largely predicted by ARICEPT<sup>®</sup>'s cholinomimetic effects. These include diarrhea, anorexia, vomiting, nausea, and echymosis. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT<sup>®</sup> treatment without the need for dose modification.

**Adverse Events Reported in Controlled Trials**  
Table 4 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT<sup>®</sup> and for which the rate of occurrence was greater for ARICEPT<sup>®</sup> assigned than placebo assigned patients.

Body System/Adverse Event	Placebo (n=392)	ARICEPT <sup>®</sup> (n=501)
<b>Percentage of Patients with any Adverse Event</b>	<b>73</b>	<b>81</b>
<b>Body as a Whole</b>		
Accident	12	13
Infection	9	11
Headache	3	4
Pain	2	3
Back Pain	2	3
Fever	2	2
<b>Cardiovascular System</b>	<1	2
Hypertension	2	3
Hemorrhage	1	2
Syncope	1	2
<b>Digestive System</b>		
Diarrhea	4	10
Vomiting	4	8
Anorexia	4	8
Nausea	2	6
<b>Hemic and Lymphatic System</b>		
Echymosis	2	5
<b>Metabolic and Nutritional Systems</b>		
Creatine Phosphokinase Increased	1	3
Dehydration	1	2
Hypertonia	<1	2
<b>Nervous System</b>		
Insomnia	4	5
Hostility	2	3
Nervousness	2	3
Hallucinations	1	3
Somnolence	1	2
Dizziness	1	2
Depression	1	2
Confusion	1	2
Emotional Lability	1	2
Personality Disorder	1	2
<b>Skin and Appendages</b>		
Eczema	2	3
<b>Urogenital System</b>		
Urinary Incontinence	1	2

**Other Adverse Events Observed During Clinical Trials**  
ARICEPT<sup>®</sup> has been administered to over 600 patients with severe Alzheimer's Disease during clinical trials of at least 6 months duration, including 3 double blind placebo controlled trials, one of which had an open label extension. All adverse events occurring at least twice are included, except for those already listed in Table 4. COSTART terms too general to be informative, or events less likely to be drug caused, are classified by body system and listed using the following definitions: **frequent adverse events**—those occurring in at least 17/100 patients; **infrequent adverse events**—those occurring in 1/100 to 17/100 patients. These adverse events are not necessarily related to ARICEPT<sup>®</sup> treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

**Body as a Whole:** *Frequent:* abdominal pain, asthenia, fungal infection, flu syndrome; *Infrequent:* allergic reaction, cellulitis, malaise, sepsis, face edema, hernia.

**Cardiovascular System:** *Frequent:* hypertension, bradycardia, ECG abnormal, heart failure; *Infrequent:* myocardial infarction, angina pectoris, atrial fibrillation, congestive heart failure, peripheral vascular disorder, supraventricular extrasystoles, ventricular extrasystoles, cardiomyopathy.

**Digestive System:** *Frequent:* constipation, gastroenteritis, fecal incontinence, dyspepsia; *Infrequent:* gamma glutamyl transpeptidase increase, gastritis, dysphagia, peribronchitis, stomach ulcer, periodontal abscess, flatulence, liver function tests abnormal, eructation, esophagitis, rectal hemorrhage.

**Endocrine System:** *Infrequent:* diabetes mellitus.

**Hemic and Lymphatic System:** *Frequent:* anemia; *Infrequent:* leukocytosis.

**Metabolic and Nutritional Disorders:** *Frequent:* weight loss, peripheral edema, edema, lactic dehydrogenase

increased, alkaline phosphatase increased; *Infrequent:* hypercholesterolemia, hypokalemia, hypoglycemia, weight gain, bilirubinemia, BUN increased, B12 deficiency anemia, cachexia, creatinine increased, gout, hyponatremia, hypoproteinemia, iron deficiency anemia, SGOT increased.

**Musculoskeletal System:** *Frequent:* arthritis; *Infrequent:* arthralgia, bone fracture, arthralgia, leg cramps, osteoporosis, myalgia.

**Nervous System:** *Frequent:* agitation, anxiety, tremor, convulsion, wandering, abnormal gait; *Infrequent:* apathy, vertigo, delusions, abnormal dreams, cerebrovascular accident, increased salivation, axata, euphoria, vasodilatation, cerebral hemorrhage, cerebral infarction, cerebral ischemia, dementia, extrapyramidal syndrome, grand mal convulsion, hemiplegia, hyperaesthesia, hypoaesthesia.

**Respiratory System:** *Frequent:* pharyngitis, pneumonia, cough increased, bronchitis; *Infrequent:* dyspnea, rhinitis, asthma, skin, sweating, urticaria, vesiculobullous rash.

**Skin and Appendages:** *Frequent:* rash, skin ulcer, pruritus; *Infrequent:* psoriasis, skin discoloration, herpes zoster, dry skin.

**Special Senses:** *Infrequent:* conjunctivitis, glaucoma, abnormal vision, ear pain, lacrimation disorder.

**Urogenital System:** *Frequent:* urinary tract infection, cystitis, hematuria, glycosuria; *Infrequent:* vaginitis, dysuria, urinary frequency, albuminuria.

**Postinfectious Reports**  
Voluntary reports of adverse events temporally associated with ARICEPT<sup>®</sup> 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, hypoproteinemia, neuroleptic malignant syndrome, pancreatitis, and rash.

**OVERDOSE USAGE**  
**Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.**  
As in any case of overdose, general supportive measures should be utilized. Overdose 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. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT<sup>®</sup> 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<sup>®</sup> and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration).

Dose-related signs of toxicity in animals included reduced spontaneous movement, proreoposition, staggering gait, incontinence, clonic convulsions, depressed respiration, salivation, tremor, emesis, fasciculation and lower body surface temperature.

**DOSEAGE AND ADMINISTRATION**  
**Mild to Moderate Alzheimer's Disease**  
The dosages of ARICEPT<sup>®</sup> shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day. The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analysis of data from these clinical trials, that a daily dose of 10 mg or ARICEPT<sup>®</sup> might provide additional benefit for some patients. Accordingly, whether or not to give a dose of 10 mg is a matter of prescriber and patient preference.

**Severe Alzheimer's Disease**  
ARICEPT<sup>®</sup> has been shown to be effective in controlled clinical trials at a dose of 10 mg administered once daily. Evidence from the controlled trials in mild to moderate Alzheimer's Disease indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, a dose of 10 mg should not be achieved until patients have been on a daily dose of 5 mg for 4 to 6 weeks.

ARICEPT<sup>®</sup> should be taken in the evening, just prior to retiring. ARICEPT<sup>®</sup> can be taken with or without food. Allow ARICEPT<sup>®</sup> ODT tablet to dissolve on the tongue and follow with water.

**HOW SUPPLIED**  
ARICEPT<sup>®</sup> is supplied as film-coated, round tablets containing either 5 mg or 10 mg of donepezil hydrochloride. The 5 mg tablets are white. The strength, in mg (5), is debossed on one side and ARICEPT is debossed on the other side. The 10 mg tablets are yellow. The strength, in mg (10), is debossed on one side and ARICEPT is debossed on the other side.

5 mg (White) Bottles of 30 (NDC# 62856-245-30)  
Bottles of 90 (NDC# 62856-245-90)  
Bottles of 1000 (NDC# 62856-245-11)  
Unit Dose Blister Package 100 (10x10) (NDC# 62856-245-41)

10 mg (Yellow) Bottles of 30 (NDC# 62856-246-30)  
Bottles of 90 (NDC# 62856-246-90)  
Bottles of 1000 (NDC# 62856-246-11)  
Unit Dose Blister Package 100 (10x10) (NDC# 62856-246-41)

ARICEPT<sup>®</sup> ODT is supplied as tablets containing either 5 mg or 10 mg of donepezil hydrochloride. The 5 mg orally disintegrating tablets are white. The strength, in mg (5), is embossed on one side and ARICEPT is embossed on the other side.

The 10 mg orally disintegrating tablets are yellow. The strength, in mg (10), is embossed on one side and ARICEPT is embossed on the other side.

Unit Dose Blister Package 30 (10x3) (NDC# 62856-831-30)  
Unit Dose Blister Package 30 (10x3) (NDC# 62856-832-30)

**Storage:** Store at controlled room temperature, 15°C to 30°C (59°F to 86°F).

**Rx only**  
ARICEPT<sup>®</sup> is a registered trademark of Eisai Co., Ltd.

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