

IMPLEMENTING HEALTH REFORM

The Center for Medicare and Medicaid Innovation

Next year, the federal government will launch the Center for Medicare and Medicaid Innovation, a new department to oversee the portfolio of payment pilot projects called for under the Affordable Care Act. As part of its charge, the innovation center will develop and evaluate pilot projects for new and old payment ideas that include accountable care organizations,

patient-centered medical homes, bundled payments, and capitated payments. Officials at the new center, one of the Centers for Medicare and Medicaid Services (CMS), will have the authority to extend or expand projects that show the potential to improve quality or cut costs.

Stuart Guterman, who studies payment policies for the Commonwealth Fund, explains the potential and the chal-

lenges for officials leading the new innovation center.

CLINICAL NEUROLOGY NEWS: Why did lawmakers create this innovation center as part of the Affordable Care Act? Is it necessary?

Mr. Guterman: I think it is necessary. I think, in fact, it may turn out to be one of the most important provisions in the

law. It focuses the attention of the CMS, which runs the two biggest health programs in the country, on the notion of innovation. It emphasizes the idea that we need to try new approaches to both payment and delivery of health care to get out off the path that we're on, which is leading to ever-growing health care costs and more pressure on the health care system.

Brief Summary—see package insert for full prescribing information.

ARICEPT® (Donepezil Hydrochloride) Tablets

ARICEPT® ODT (Donepezil Hydrochloride) Orally Disintegrating Tablets

INDICATIONS AND USAGE ARICEPT is indicated for the treatment of dementia of the Alzheimer's type. Efficacy has been demonstrated in patients with mild, moderate, and severe Alzheimer's Disease. **DOSAGE AND ADMINISTRATION** ARICEPT should be taken in the evening, just prior to retiring. ARICEPT can be taken with or without food and should be swallowed whole with water. ARICEPT should not be split or crushed. The 23 mg tablet should not be crushed or chewed because this may increase its rate of absorption. Allow ARICEPT ODT tablet to dissolve on the tongue and follow with water. **Mild to Moderate Alzheimer's Disease:** The dosages of ARICEPT 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 analyses of data from these clinical trials, that a daily dose of 10 mg of ARICEPT might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference. **Moderate to Severe Alzheimer's Disease:** ARICEPT has been shown to be effective in controlled clinical trials at doses of 10 mg and 23 mg administered once daily. Results of a controlled clinical trial in moderate to severe Alzheimer's Disease that compared ARICEPT 23 mg once daily to 10 mg once daily suggest that a 23 mg dose of ARICEPT provided additional benefit. **Titration:** The recommended starting dose of ARICEPT is 5 mg 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 compared to the 5 mg dose. In open-label trials using a 6 week titration, the type and frequency of these same adverse events were similar between the 5 mg and 10 mg dose groups. Therefore, because ARICEPT steady state is achieved about 15 days after it is started and because the incidence of untoward effects may be influenced by the rate of dose escalation, a dose of 10 mg should not be administered until patients have been on a daily dose of 5 mg for 4 to 6 weeks. A dose of 23 mg once daily can be administered once patients have been on a dose of 10 mg once daily for at least 3 months. **CONTRAINDICATIONS** ARICEPT is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS AND PRECAUTIONS Anesthesia:** 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. Syncope episodes have been reported in association with the use of ARICEPT. **Nausea and Vomiting:** 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, and more frequently with the 23 mg dose than with the 10 mg dose. Specifically, in a controlled trial that compared a dose of 23 mg/day to 10 mg/day in patients who had been treated with donepezil 10 mg/day for at least three months, the incidence of nausea in the 23 mg group was markedly greater than in the patients who continued on 10 mg/day (11.8% vs 3.4%, respectively), and the incidence of vomiting in the 23 mg group was markedly greater than in the 10 mg group (9.2% vs 2.5%, respectively). The percent of patients who discontinued treatment due to vomiting in the 23 mg group was markedly higher than in the 10 mg group (2.9% vs 0.4%, respectively). Although in most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT, patients should be observed closely at the initiation of treatment and after dose increases. **Peptic Ulcer Disease and GI Bleeding:** 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 in a dose of 5 mg/day to 10 mg/day have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. Results of a controlled clinical study with 23 mg/day showed an increase, relative to 10 mg/day, in the incidence of peptic ulcer disease (0.4% vs. 0.2%) and gastrointestinal bleeding from any site (1.1% vs. 0.6%). **Weight Loss:** Weight loss was reported as an adverse event in 4.7% of patients assigned to ARICEPT in a dose of 23 mg/day compared to 2.5% of patients assigned to 10 mg/day. Compared to their baseline weights, 8.4% of patients taking 23 mg/day were found to have a weight decrease of $\geq 7\%$ by the end of the study, while 4.9% of patients taking 10 mg/day were found to have weight loss of $\geq 7\%$ at the end of the study. **Genitourinary Conditions:** Although not observed in clinical trials of ARICEPT, cholinomimetics may cause bladder outflow obstruction. **Neurological Conditions: Seizures:** Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's disease. **Pulmonary Conditions:** Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **ADVERSE REACTIONS Clinical Studies Experience: ARICEPT 5 mg/day and 10 mg/day Mild to Moderate Alzheimer's Disease 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 7-day escalations 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 or more the incidence seen in placebo patients, are shown in Table 1. **Table 1. Most Frequent Adverse Events Leading to Discontinuation from Controlled Clinical Trials by Dose Group (Placebo, 5 mg/day ARICEPT, and 10 mg/day ARICEPT, respectively); Patients Randomized (355, 350, 315); Event/% Discontinuing:** Nausea (1%, 1%, 3%); Diarrhea (0%, <1%, 3%); Vomiting (<1%, <1%, 2%). **Most Frequent Adverse 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 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 269 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. **Table 2. Comparison of Rates of Adverse Events in Mild to Moderate Patients Titrated to 10 mg/day over 1 and 6 Weeks (No titration: Placebo [n=315], No titration: 5 mg/day [n=311], One week titration: 10 mg/day [n=315], Six week titration: 10 mg/day [n=269], respectively):** 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 that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT and for which the rate of occurrence was greater for patients treated with ARICEPT than with placebo. 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 and at a Higher Frequency than Placebo Treated Patients (Body System/ Adverse Event: Placebo [n=355], ARICEPT [n=747], respectively): 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 System:** Ecchymosis (3, 4). **Metabolic and Nutritional Systems:** Weight Decrease (1, 3). **Musculoskeletal System:** Muscle Cramps (2, 6); Arthritis (1, 2). **Nervous System:** Insomnia (6, 9); Dizziness (6, 8); Depression (<1, 3); Abnormal Dreams (0, 3); Somnolence (<1, 2). **Urogenital System:** Frequent Urination (1, 2). **Other Adverse Events Observed During Clinical Trials** ARICEPT 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 three 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. 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 related. Events are classified by body system and listed using the following definitions: *Frequent adverse events* - those occurring in at least 1/100 patients; *Infrequent adverse events* - those occurring in 1/100 to 1/1000 patients. 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. No important additional adverse events were seen in studies conducted outside the United States. **Body as a Whole:** *Frequent:* influenza, chest pain, toothache; *Infrequent:* fever, edema face, periorbital edema, hernia hiatal, 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, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis. **Digestive System:** *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* 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:** *Infrequent:* diabetes mellitus, gout. **Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocytopenia, thrombocytopenia, eosinophilia, erythrocytopenia. **Metabolic and Nutritional Disorders:** *Frequent:* dehydration; *Infrequent:* gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. **Musculoskeletal System:** *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation. **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, hypertension, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. **Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. **Skin and Appendages:** *Frequent:* pruritus, diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* 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:** *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, 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 due to adverse events for the ARICEPT 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 patients and at twice or more the incidence seen in placebo, 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 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 ARICEPT and at twice or more the placebo rate, are largely predicted by ARICEPT's cholinomimetic effects. These include diarrhea, anorexia, vomiting, nausea, and ecchymosis. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT treatment without the need for dose modification. **Adverse Events Reported in Controlled Trials** Table 4 lists adverse events that were

We already spend 50% more than any other country in the world on health care. Everybody points to the amount of waste in the system. But it's harder to identify ways of actually getting rid of it and making the health care system work better for people. That's what this innovation center was intended to do – to focus the attention of the federal government on that issue and to bring in the other parts of the health care sector to collaborate on better ways of providing care and better ways of paying for care.

CNN: Some of the concepts – such as medical homes and capitated payments – have been tested before. What makes

The Center 'may turn out to be one of most important provisions in the law [because] it emphasizes the idea that we need to try new approaches to both payment and delivery of health care.'

this effort different?

Mr. Guterman: Capitation was tried in the 1990s, but the world was a different

place then. In the 1990s, we didn't have the kinds of measures of health system performance that we have now. Also, the notion of capitating payments so that you provided a strong incentive to reduce costs got separated from the notion of providing care in an effective, efficient way. So we started out with a managed care movement that was focused on providing coordinated care for patients and we ended up with a movement that was focused primarily on reducing the costs, sometimes in arbitrary ways. To-

day, I think we have the tools to avoid going off that track. We may not get all the way to capitation, but there are bundled payments and other strategies that get us away from the current fee-for-service system.

In terms of the medical home, models are being tested by various private payers, Medicare is developing a demonstration project, and Medicaid is testing several models. But those efforts are fragmented, just like the rest of our health care delivery and financing systems. If we conduct these pilots individually, they are much less effective than if they can be coordinated and focused, using the same kinds of measures.

CNN: What are the keys to making the innovation center successful?

Mr. Guterman: We need to bring to-



Pilot payment projects must be coordinated and focused, using the same kinds of measures, if they are to be effective.

MR. GUTERMAN

gether all of the health care system's stakeholders. We are currently projected to spend between \$30 trillion and \$35 trillion on health care over the next 10 years. The issue is not what to cut, it's how to use some reasonable amount of money to buy the kind of health care we think our system should produce. That requires the involvement of everyone – providers, patients, and public and private payers.

CNN: What challenges will officials at the Center for Medicare and Medicaid Innovation face in rapidly testing new payment concepts?

Mr. Guterman: It's easy to say that everyone ought to be involved, but right now people tend to look at change as something that threatens them. We need to overcome that.

We also need to have patience. A lot of these projects will take time to develop and implement, and to adjust as they go along. But Congress and the American public also need to have patience and realize these strategies will take awhile to unfold.

CNN: Is the center's work likely to have a significant impact on lowering costs?

Mr. Guterman: Yes, though it's hard to predict just how much. You've got a system now that pays for more care, more complicated care, and more invasive care, but not more appropriate and efficient care. So you've got to figure that if you change the focus from more to better and from more invasive to more appropriate, that you can make some difference in lowering costs. ■

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reported in at least 2% of patients in placebo-controlled trials who received ARICEPT and for which the rate of occurrence was greater for patients treated with ARICEPT than with placebo. **Table 4. Adverse Events Reported in Controlled Clinical Trials in Severe Alzheimer's Disease in at Least 2% of Patients Receiving ARICEPT and at a Higher Frequency than Placebo Treated Patients (Body System/Adverse Event: Placebo [n=392], ARICEPT [n=501], respectively): Percent of Patients with any Adverse Event: 73, 81. Body as a Whole:** Accident (12, 13); Infection (9, 11); Headache (3, 4); Pain (2, 3); Back Pain (2, 3); Fever (1, 2); Chest Pain (<1, 2). **Cardiovascular System:** Hypertension (2, 3); Hemorrhage (1, 2); Syncope (1, 2). **Digestive System:** Diarrhea (4, 10); Vomiting (4, 8); Anorexia (4, 8); Nausea (2, 6). **Hemic and Lymphatic System:** Ecchymosis (2, 5). **Metabolic and Nutritional System:** Creatine Phosphokinase Increased (1, 3); Dehydration (1, 2); Hyperlipemia (<1, 2). **Nervous System:** 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). **Skin and Appendages:** Eczema (2, 3). **Urogenital System:** Urinary Incontinence (1, 2). **Other Adverse Events Observed During Clinical Trials** ARICEPT has been administered to over 600 patients with severe Alzheimer's disease during clinical trials of at least 6 months duration, including three double-blind placebo-controlled trials, two 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 related. Events are classified by body system using the COSTART dictionary and listed using the following definitions: **Frequent adverse events** - those occurring in at least 1/100 patients; **Infrequent adverse events** - those occurring in 1/100 to 1/1000 patients. 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. **Body as a Whole:** Frequent: abdominal pain, asthenia, fungal infection, flu syndrome; Infrequent: allergic reaction, cellulitis, malaise, sepsis, face edema, hernia. **Cardiovascular System:** Frequent: hypotension, bradycardia, ECG abnormal, heart failure; Infrequent: myocardial infarction, angina pectoris, atrial fibrillation, congestive heart failure, peripheral vascular disorder, supraventricular extrasystoles, ventricular extrasystoles, cardiomegaly. **Digestive System:** Frequent: constipation, gastroenteritis, fecal incontinence, dyspepsia; Infrequent: gamma glutamyl transpeptidase increase, gastritis, dysphagia, periodontitis, 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: hypercholesteremia, hypokalemia, hypoglycemia, weight gain, bilirubinemia, BUN increased, B₁₂ deficiency anemia, cachexia, creatinine increased, gout, hyponatremia, hypoproteinemia, iron deficiency anemia, SGOT increased, SGPT increased. **Musculoskeletal System:** Frequent: arthritis; Infrequent: arthrosis, 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, ataxia, euphoria, vasodilatation, cerebral hemorrhage, cerebral infarction, cerebral ischemia, dementia, extrapyramidal syndrome, grand mal convulsion, hemiplegia, hypertension, hypokinesia. **Respiratory System:** Frequent: pharyngitis, pneumonia, cough increased, bronchitis; Infrequent: dyspnea, rhinitis, asthma. **Skin and Appendages:** Frequent: rash, skin ulcer, pruritus; Infrequent: psoriasis, skin discoloration, herpes zoster, dry skin, sweating, urticaria, vesiculobullous rash. **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. **ARICEPT 23 mg/day Moderate to Severe Alzheimer's Disease** ARICEPT 23 mg/day has been administered to over 1300 individuals globally in clinical trials. Approximately 1050 of these patients have been treated for at least three months and more than 950 patients have been treated for at least six months. The range of patient exposure was from 1 to over 500 days. **Adverse Events Leading to Discontinuation** The rate of discontinuation from a controlled clinical trial of ARICEPT 23 mg/day due to adverse events was higher (18.6%) than for the 10 mg/day treatment group (7.9%). The most common adverse events leading to discontinuation, defined as those occurring in at least 1% of patients and greater than those occurring with 10 mg/day are shown in Table 5. **Table 5. Most Frequent Adverse Events Leading to Discontinuation from a Controlled Clinical Trial by Treatment Group (Dose Group: 23 mg/day ARICEPT, 10 mg/day ARICEPT, respectively): Safety Population: 963, 471. Event/%Discontinuing:** Vomiting (3, 0); Diarrhea (2, 0); Nausea (2, 0); Dizziness (1, 0). The majority of discontinuations due to adverse events in the 23 mg group occurred during the first month of treatment. **Most Frequent Adverse Events Seen in Association with the Use of 23 mg/day** The most common adverse events, defined as those occurring at a frequency of at least 5%, include nausea, diarrhea, vomiting, and anorexia. These adverse events were often of mild to moderate intensity. **Adverse Events Reported in Controlled Trials** The events cited reflect experience gained under closely monitored conditions of a controlled clinical trial 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 6 lists adverse events that were reported in at least 2% of patients who received 23 mg/day of ARICEPT and at a higher frequency than those receiving 10 mg/day of ARICEPT in a controlled clinical trial that compared the two doses. In this study, there were no important differences in the type of adverse events in patients taking ARICEPT with or without memantine. **Table 6. Adverse Events Reported in a Controlled Clinical Trial in Moderate to Severe Alzheimer's Disease in at Least 2% of Patients and Higher in the 23 mg/day Group (Body System/Adverse Event: 23 mg/day ARICEPT, 10 mg/day ARICEPT, respectively): Safety Population: 963, 471. Percent of Patients with any Adverse Event: 74, 64. Gastrointestinal disorders:** Nausea (12, 3); Vomiting (9, 3); Diarrhea (8, 5). **General disorders and administration site conditions:** Fatigue (2, 1); Asthenia (2, 1). **Injury, poisoning and procedural complications:** Contusion (2, 0). **Investigations:** Weight decreased (5, 3). **Metabolism and nutrition disorders:** Anorexia (5, 2). **Nervous system:** Dizziness (5, 3); Headache (4, 3); Somnolence (2, 1). **Psychiatric disorders:** Insomnia (3, 2). **Renal and urinary disorders:** Urinary incontinence (3, 1). **Postmarketing Experience:** Voluntary reports of adverse events temporally associated with ARICEPT that have been received since market introduction that are not listed above, and for which there are 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, neuroleptic malignant syndrome, pancreatitis, and rash. **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 K_i about 50-130

μM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT has any potential for enzyme induction is not known. Formal pharmacokinetic studies evaluated the potential of ARICEPT for interaction with theophylline, cimetidine, warfarin, 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 (AUC₀₋₂₄ and C_{max}) by 36%. The clinical relevance of this increase in concentration is unknown. A small effect of CYP2D6 inhibitors was identified in a population pharmacokinetic analysis of plasma donepezil concentrations measured in patients with Alzheimer's disease. Donepezil clearance was reduced by approximately 17% in patients taking 10 or 23 mg in combination with a known CYP2D6 inhibitor. This result is consistent with the conclusion that CYP2D6 is a minor metabolic pathway of donepezil. 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. **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 IN SPECIFIC POPULATIONS Pregnancy: Pregnancy Category C:** 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. Oral administration of donepezil to pregnant rats and rabbits during the period of organogenesis did not produce any teratogenic effects at doses up to 16 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] of 23 mg/day on a mg/m² basis) and 10 mg/kg/day (approximately 7 times the MRHD on a mg/m² basis), respectively. Oral administration of donepezil (1, 3, 10 mg/kg/day) to rats during late gestation and throughout lactation to weaning produced an increase in stillbirths and reduced offspring survival through postpartum day 4 at the highest dose. The no-effect dose of 3 mg/kg/day is approximately equal to the MRHD on a mg/m² basis. **Nursing Mothers:** It is not known whether donepezil is excreted in human breast milk. Caution should be exercised when ARICEPT is administered to a nursing woman. **Pediatric Use:** The safety and effectiveness of ARICEPT in children have not been established. **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 73 years; 80% of these patients were between 65 and 84 years old, and 49% of 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. **Lower Weight Individuals:** In the controlled clinical trial, among patients in the ARICEPT 23 mg treatment group, those patients weighing < 55 kg reported more nausea, vomiting, and decreased weight than patients weighing 55 kg or more. There were more withdrawals due to adverse events as well. This finding may be related to higher plasma exposure associated with lower weight. **OVERDOSAGE 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. 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. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT 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 in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature. **NONCLINICAL TOXICOLOGY 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 on a mg/m² basis), 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/m² 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/m² basis).



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