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CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

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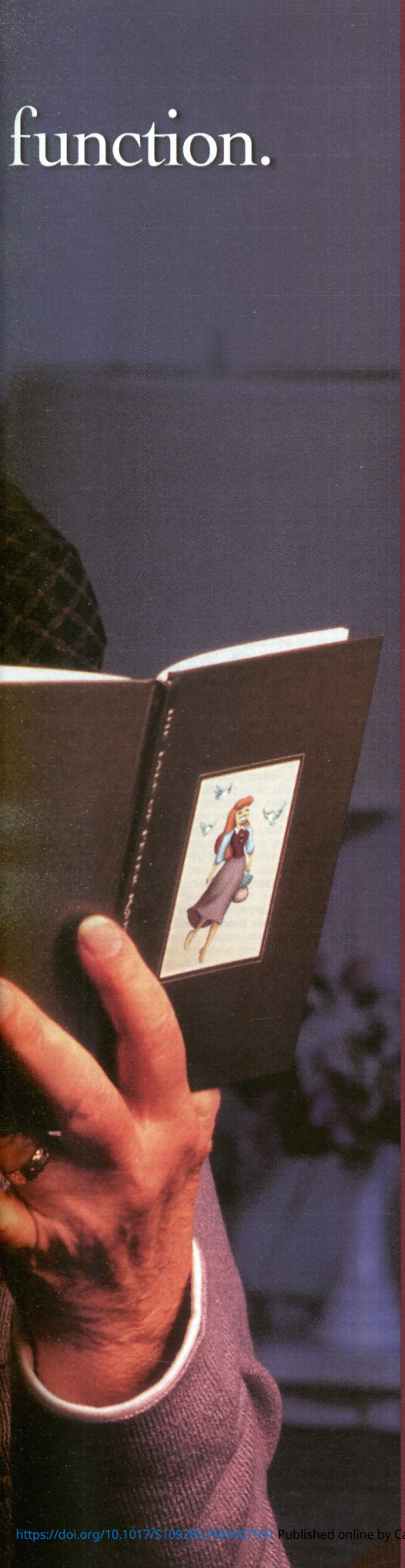
* *Individual responses to ARICEPT® may include improvement, stabilization, or decline.*

† The most common adverse events in pivotal clinical trials with ARICEPT® were nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia. Pivotal clinical trials of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. Nevertheless, cholinesterase inhibitors may be expected to increase gastric acid secretion. Therefore, patients (especially those at increased risk for developing ulcers—eg, having a history of ulcer disease, receiving concurrent nonsteroidal anti-inflammatory drugs) should be monitored closely for gastrointestinal bleeding. In pivotal clinical trials, syncopal episodes have been reported in association with ARICEPT® (2% vs 1% for placebo).



function.

She sees it as a bedtime story.

ARICEPT®. Helping to make a difference for people living with Alzheimer's

- Slows the worsening of symptoms*
- Proven to maintain cognition in placebo-controlled studies
- Well tolerated†
- Proven safety profile
- Once-daily dosing
- 3 years of real-world use

ONCE-A-DAY

ARICEPT®

(donepezil HCl)

5-MG AND 10-MG TABLETS

THERAPY TO REMEMBER™

Please see brief summary of prescribing information on adjacent page.

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EL208A99CR

60-Day Planner

MEETINGS **DEADLINES** **REMINDERS**

July

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1	*2*	*3*	*4* *Independence Day—USA*	*5* International Neuropsychological Society: 23rd Midyear Meeting, Brasilia, DF, Brazil **(July 4–7)** *contact:* Tel: 614.263.4200 Fax: 614.263.4366	*6*	*7 (–10)* Focus on Epilepsy VI: Treatment of Epileptic Syndromes from Molecular Targets to Quality of Life: Chateau Mont-Tremblet, QC, Canada *contact:* Tel: 514.933.0502 eriplus@total.net
8	*9* 2001— A Mind Odyssey: Science and Caring: London, UK *contact:* Tel: 44.20.72.35.23.51 x142 mbraithwaite@ rcpsych.ac.uk	*10*	*11 (–15)* Annual Convention of the National Alliance for the Mentally Ill: Washington, DC *contact:* Tel: 800.950.6264 Fax: 703.524.9094	*12 (–14)* 2001 Conference of the Stress and Anxiety Research Society: Majorca, Spain *contact:* Tel: 34.971.173.038 dpsjpp0@ps.uib.es	*13*	*14*
15	*16 (–20)* 18th Annual Summer Symposium: Difficult Personality Disorder— A Comprehensive Treatment Approach, Eastham, MA *contact:* Tel: 800.926.1232	*17*	*18 (–21)* National Conference on Autism: San Diego, CA *contact:* Tel: 301.657.0881 thayes@ autism-society.org	*19 (–22)* 9th Annual Advanced Topics in CT Scanning: 2001 Edition: Lake Tahoe, NV *contact:* Tel: 410.995.2959 cmenet@jhmi.edu	*20 (–23)* Advances in Neurology: St. Petersburg, FL *contact:* Tel: 813.259.0605 sbenbadi@ hsc.usf.edu	*21 (–24)* 16th Mexican Congress of Neurological Surgery: Puerto Vallarta, Mexico *contact:* Tel: 52.55.430.013 smcirneu@dsi.com.mx
22 (–27) 26th Biennial Congress of the World Federation for Mental Health: Vancouver, Canada *contact:* Fax: 703.684.5968	*23* Mt. Sinai School of Medicine: Alzheimer's Disease, Cancer, and the Search for a Better Aspirin, New York, NY **(July 22–23)** *contact:* Tel: 212.241.6737	*24*	*25 (–27)* National Institute of Mental Health: Preventing and Adapting to HIV/AIDS, Los Angeles, CA *contact:* Tel: 301.443.611 Fax: 301.443.9719	*26*	*27 (–29)* World Events Forum, Inc.: Challenging Views of Alzheimer's Disease, Cincinnati, OH *contact:* Tel: 7.737.848.134 contact@ worldeventsforum.com	*28 (–Aug 1)* 14th International Congress on Parkinson's Disease: Helsinki, Finland *contact:* Tel: 358.945.421.933 aira@congcreator.com
29	*30*	*31*				

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60-Day Planner

August

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1 **August *CNS* closes & ships to printer**	*2* Advances and Changing Trends in Medicine: Orlando, FL **(Aug. 1–5)** *contact:* Tel: 800.462.9633 cme-jax@mayo.edu	*3* Pediatric Neurology Update: Indianapolis, IN *contact:* Tel: 317.274.8353	*4 (–8)* International Society of Psychoneuroendocrinology: Quebec City, Canada *contact:* Tel: 418.654.2152 ISPNE2001@ crchul.ulaval.ca
5	*6*	*7*	*8*	*9*	*10*	*11 (–14)* 11th Nordic Meeting on Cerebrovascular Diseases and 2nd Biennial Kuopio Symposium on Ischemic Stroke: Kuopio, Finland *contact:* Tel: 358.17.162519 jukka@jolkkonen@uku.fl
12 American Academy of Sleep: National Sleep Medicine Course, Leesburg, VA **(Aug 11–15)** *contact:* Tel: 507.287.6006 Fax: 507.287.6008	*13*	*14*	*15 (–18)* Neurological and Orthopaedic Surgery: 25 Years of Medicine and Beyond: Las Vegas, NV *contact:* Tel: 702.388.7390 aanos@lasvegas.net	*16*	*17 (–20)* Current Therapy of Peripheral Neuropathy: Rome, Italy *contact:* Tel: 520.818.0943 rome@intgrid.com	*18*
19 (–24) 14th Conference of the International Society of Magnetic Resonance: Jerusalem, Israel *contact:* Tel: 9723.6133340 x207 team1@congress.co.il	*20* 6th Multi Disciplinary Conference on Parkinson's Disease: Melbourne, Australia **(Aug 19–21)** *contact:* Tel: 61.299.568.333 mail@ conferencetion.com.au	*21*	*22*	*23*	*24 (–29)* 16th World Congress on Psychosomatic Medicine: Gothenburg, Sweden *contact:* Tel: 46.31.43.10.12 icpm.2001@swefair.se	*25* Meeting of the American Association of Neurological Surgeons: Neurosurgical Practice Management Strategies for Success, Chicago, IL *contact:* Tel: 847.378.0500 epm@aans.org
26 (–31) 32nd Annual Meeting of the American Society for Neurochemistry: Buenos Aires, Argentina *contact:* Tel: 352.271.3383	*27*	*28*	*29* **September *CNS* closes & ships to printer**	*30*	*31*	

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ARICEPT® (Donepezil Hydrochloride Tablets)

Brief Summary – see package insert for full prescribing information. **INDICATIONS AND USAGE** ARICEPT® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. **CONTRAINDICATIONS** ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS** ***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 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. 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®, 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. **PRECAUTIONS 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 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. ***Effect of Other Drugs on the Metabolism of ARICEPT®:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of these inhibitors is not known. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. ***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. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity studies of donepezil have not been completed. Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria. 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. 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). **Pregnancy *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/m² basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m² 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/m² 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. **ADVERSE REACTIONS 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 the incidence seen in placebo patients, are shown in Table 1.

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

Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®
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 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 Patients Titrated to 10 mg/day Over 1 and 6 Weeks

Adverse Event	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)
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 ARICEPT® 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 at Least 2% of Patients Receiving ARICEPT® (donepezil HCl) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=355)	ARICEPT® (n=747)
Percent of Patients with any Adverse Event	72	74
Body as a Whole		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular System		
Syncope	1	2
Digestive System		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and Lymphatic 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 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®. 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. 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, goiter. **Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocythemia, 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, hypertonia, 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. **Postintroduction 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. **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® overdosage. 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. **DOSAGE AND ADMINISTRATION** The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day. Controlled clinical trials indicated 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. Because steady state is not achieved for 15 days and because the incidence of such effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks. Whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference. ARICEPT® should be taken in the evening, just prior to retiring, and may be taken with or without food.

Revised September 1999

Eisai Inc. Teaneck, NJ 07666

Pfizer U.S. Pharmaceuticals New York, NY 10017

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In the Journal of June 2001

APPLYING CIRCADIAN RHYTHMS TO MEDICAL PRACTICE

page 467

"Improper BP control throughout the course of 24 hours can cause neurologic disorders. Twenty-four-hour BP control is the goal of antihypertensive therapy, and a large variety of different classes of medications are available to choose from to reach that goal. Most of these medicines are intended for morning ingestion, and most aim at maintaining near-constant plasma-drug concentration during the day and night. From a regulatory perspective, 24-hour BP control means that the magnitude of the BP-lowering effect at the end of the daily dosing interval (when the drug level is lowest) is 50% or more of the peak BP-lowering effect (when the drug level is highest). However, this seems to be an inadequate clinical definition because it fails to take into account all the relevant features of the circadian-BP rhythm as they relate to the risk of cardiovascular events and neurologic end-organ injury."

SEASONAL DEPRESSION AND BIOLOGICAL RHYTHMS

page 487

"A close relationship between depression and biological rhythms has long been evident. Symptoms of depression are often circadian in nature: for example, a depressed mood is typically worse in the morning and improves during the day. Sleep during depression is usually disrupted. The most usual form is insomnia in the last hours of normal sleep, or early morning awakening. In sleep recordings, a reduced time of onset of rapid eye movement sleep (REM latency) is frequently found. Other patients may have insomnia in the initial and/or middle phases of sleep, while others may have insomnia in all three phases of sleep: initial, middle, and terminal. Depressed patients may show increased sleep (hypersomnia), falling asleep too early, or sleeping too late. Furthermore, a relationship between depression and seasonal rhythms has also been long noted. Episodes of depression are most likely to start in the spring or fall, with some patients having repeated recurrences of depression beginning in the spring or fall, but rarely both. Patients with winter SAD—a specific type of seasonal depression—experience recurrent episodes of depression beginning in the fall and ending in the spring."

IRREGULAR MELATONIN LEVELS AND SLEEP DIFFICULTIES IN THE ELDERLY

page 502

"Previous studies of age-related changes in melatonin production found reduced serum melatonin concentrations in old age. Delayed nocturnal melatonin onset and peak time have also been reported in old age. However, none of these studies distinguished between elderly people without sleep complaints and those suffering from sleep disorders. In recent years, our laboratory has been involved in a large-scale project aimed at investigating the role of endogenous melatonin in sleep-wake regulation and the effects of pharmacologic levels of melatonin on sleep in the elderly."

FLUVOXAMINE LINKED TO SLEEP DISORDERS?

page 511

"Clinically, it is advised for doctors treating patients with psychotropic drugs, especially SSRIs and FVA, to take into consideration CRSD as a possible side effect. Often when psychotropic drugs are prescribed, a side effect of sleep difficulty is diagnosed under the general heading of insomnia. As we have shown, the new onset of a sleep problem may well be CRSD, which can be fairly easily diagnosed and confirmed, and often simply treated by changing the implicated drug prescribed or adding melatonin."

HEAVY SMOKING AND SCHIZOPHRENIA

page 514

"The mentally ill smoke at a rate higher than the general population. Patients with chronic schizophrenia smoke at a rate approaching 90%, while lifetime smoking rates for the general community are about 18%. Glassman and colleagues suggested that chronic smoking is associated with a reduction in the firing of nigrostriatal dopaminergic neurons in the absence of changes in the numbers of dopamine receptors and in the dopamine transporter. The reduced dopamine turnover associated with the increased numbers of high-affinity nicotine receptors is consistent with the attenuated efficacy of these receptors in smokers. Many investigators have supported an early processing deficit in schizophrenia. There is a significant association between the missing peaks of the auditory brainstem responses and the Brief Psychiatric Rating Scale (BPRS) negative-symptom cluster or the total score of the scale of assessment of negative symptoms (SANS). This suggests that some patients with schizophrenia, especially those with negative symptoms, have an abnormality in the input processing of auditory information in the lower brainstem. Igata and colleagues, on the other hand, found that smoking affects brainstem auditory evoked potentials (BAEPs) through many mechanisms."

ONCE-DAILY
PAXIL
PAROXETINE HCl

References: 1. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR™*. 4th ed. Washington, DC: American Psychiatric Association; 2000. **2.** Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement on generalised anxiety disorder. *In press.* **3.** Paxil® (paroxetine HCl) Prescribing Information.

PAXIL® (brand of paroxetine hydrochloride)
See complete prescribing information in SmithKline Beecham Pharmaceuticals literature. The following is a brief summary.

INDICATIONS AND USAGE: *Paxil* is indicated for the treatment of depression, obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in DSM-IV, panic disorder, with or without agoraphobia, as defined in DSM-IV, social anxiety disorder, as defined in DSM-IV, and generalized anxiety disorder, as defined in DSM-IV.

CONTRAINDICATIONS: Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated. (See WARNINGS and PRECAUTIONS.) Contraindicated in patients with a hypersensitivity to paroxetine or any of the inactive ingredients in *Paxil*.

WARNINGS: Interactions with MAOIs may occur. Given the fatal interactions reported with concomitant or immediately consecutive administration of MAOIs and other SSRIs, do not use *Paxil* in combination with a MAOI or within 2 weeks of discontinuing MAOI treatment. Allow at least 2 weeks after stopping *Paxil* before starting a MAOI.

Potential Interaction with Thioridazine

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes-type arrhythmias, and sudden death. This *effect appears to be dose related.*

An *in vivo* study suggests that drugs which inhibit $P_{450}IID_6$, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine.

PRECAUTIONS: As with all antidepressants, use *Paxil* cautiously in patients with a history of mania.

Use *Paxil* cautiously in patients with a history of seizures. Discontinue it in any patient who develops seizures.

The possibility of suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Write *Paxil* prescriptions for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Reversible hyponatremia has been reported, mainly in elderly patients, patients taking diuretics or those who were otherwise volume depleted. Abnormal bleeding (mostly ecchymosis and purpura), including a case of impaired platelet aggregation, has been reported; the relationship to paroxetine is unclear.

Clinical experience with *Paxil* in patients with concomitant systemic illness is limited. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Observe the usual cautions in cardiac patients. In patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment, a lower starting dose (10 mg) should be used.

Caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that *Paxil* therapy does not affect their ability to engage in such activities. Tell patients 1) to continue therapy as directed; 2) to inform physicians about other medications they are taking or plan to take; 3) to avoid alcohol while taking *Paxil*; 4) to notify their physicians if they become pregnant or intend to become pregnant during therapy, or if they're nursing.

Weakness, hyperreflexia, and incoordination following use of an SSRI and sumatriptan have been rarely reported.

Concomitant use of *Paxil* with tryptophan is not recommended. Use cautiously with warfarin. When administering *Paxil* with cimetidine, dosage adjustment of *Paxil* after the 20 mg starting dose should be guided by clinical effect. *When co-administering Paxil with phenobarbital or phenytoin, no initial Paxil dosage adjustment is needed; base* subsequent changes on clinical effect. Concomitant use of *Paxil* with drugs metabolized by cytochrome $P_{450}IID_6$ (antidepressants such as nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine; phenothiazines; Type 1C antiarrhythmics such as propafenone, fecainide and encainide) or with drugs that inhibit this enzyme (e.g., quinidine) may require lower doses than usually prescribed for either *Paxil* or the other drug; approach concomitant *use cautiously. However, due to the risk of serious ventricular arrhythmias and sudden death potentially* associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be co-administered. An *in vivo* interaction study revealed that paroxetine had no effect on terfenadine pharmacokinetics. Additional *in vitro* studies showed that the inhibitory effects of paroxetine on other $IIIA_4$ substrates (astemizole, cisapride, triazolam and cyclosporin) was at least 100 times less potent than ketoconazole, a potent $IIIA_4$ inhibitor. Assuming *that the relationship between paroxetine's in vitro Ki and its lack of effect on terfenadine's in vivo clearance* predicts its effect on other $IIIA_4$ substrates, paroxetine's inhibition of $IIIA_4$ activity should have little clinical significance. Use caution when co-administering *Paxil* with tricyclic antidepressants (TCAs). TCA plasma concentrations may need monitoring and the TCA dose may need to be reduced. Administration of *Paxil* with another tightly protein-bound drug may shift plasma concentrations, resulting in adverse effects from either drug. Concomitant use of *Paxil* and alcohol in depressed patients is not advised. Undertake concomitant use of *Paxil* and lithium or digoxin cautiously. If adverse effects are seen when co-administering *Paxil* with procyclidine, reduce the procyclidine dose. Elevated theophylline levels have been reported with *Paxil* co-administration; monitoring theophylline levels is recommended.

In 2-year studies, a significantly greater number of male rats in the 20 mg/kg/day group developed reticulum cell *sarcomas vs. animals given doses of 1 or 5 mg/kg/day. There was also a significantly increased linear trend across* dose groups for the occurrence of lymphoreticular tumors in male rats. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The clinical significance of these findings is unknown. There is no evidence of mutagenicity with *Paxil*.

Rats receiving paroxetine at 15 mg/kg/day (2.4 times the MRHD on a mg/m^2 basis) showed a reduced pregnancy *rate.*

Pregnancy Category C. Reproduction studies performed in rats and rabbits at doses up to 6 mg/kg/day, 8.1 (rat) and 1.9 (rabbit) times the MRHD on a mg/m^2 basis, have revealed no evidence of teratogenic effects or of selective toxicity to the fetus. However, rat pup deaths increased during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. The cause of these deaths is not known. *There are no adequate and well-controlled studies in pregnant women. Paxil should be used in pregnancy only if* the potential benefit justifies the potential risk to the fetus. The effect of *Paxil* on labor and delivery in humans is unknown. Paroxetine is secreted in human milk; exercise caution when administering *Paxil* to a nursing woman.

Safety and effectiveness in the pediatric population have not been established.

In worldwide premarketing *Paxil* clinical trials, 17% of *Paxil*-treated patients were ≥65 years of age. Pharmacokinetic studies revealed a decreased clearance in the elderly and a lower starting dose is recommended. However, there were no overall differences in the adverse event profile between older and younger patients.

ADVERSE REACTIONS: Incidence in Controlled Trials—*Commonly Observed Adverse Events in Controlled Clinical Trials:* The most commonly observed adverse events associated with the use of *Paxil* in the treatment of depression (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo): asthenia (15% vs. 6%), sweating (11% vs. 2%), nausea (26% vs. 9%), decreased appetite (6% vs. 2%), somnolence (23% vs. 9%), dizziness (13% vs. 6%), insomnia (13% vs. 6%), tremor (8% vs. 2%), nervousness (5% vs. 3%), ejaculatory disturbance (13% vs. 0%) and other male genital disorders (10% vs. 0%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of obsessive compulsive disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that of placebo) were: nausea (23% vs. 10%), dry mouth (18% vs. 9%), decreased appetite (9% vs. 3%), constipation (16% vs. 6%), dizziness (12% vs. 6%), somnolence (24% vs. 7%), tremor (11% vs. 1%), sweating (9% vs. 3%), impotence (8% vs. 1%) and abnormal ejaculation (23% vs. 1%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of panic disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo) were: asthenia (14% vs. 5%), sweating (14% vs. 6%), decreased appetite (7% vs. 3%), libido decreased (9% vs. 1%), tremor (9% vs. 1%), abnormal ejaculation (21% vs. 1%), female genital disorders (9% vs. 1%) and impotence (5% vs. 0%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of social anxiety disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo) were: sweating (9% vs. 2%), nausea (25% vs. 7%), dry mouth (9% vs. 3%), constipation (5% vs. 2%), decreased appetite (8% vs. 2%), somnolence (22% vs. 5%), tremor (9% vs. 1%), libido decreased (12% vs. 1%), yawn (5% vs. 1%), abnormal ejaculation (28% vs. 1%), female genital disorders (9% vs. 1%) and impotence (5% vs. 1%).

The most commonly observed adverse events associated with the use of paroxetine in the treatment of generalized anxiety disorder (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo) were: asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

Twenty percent (1,199/6,145) of *Paxil* patients in worldwide clinical trials in depression and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469) and 10.7% (79/735) of *Paxil* patients in worldwide trials in social anxiety disorder, OCD, panic disorder and generalized anxiety disorder, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related include the following: **depression**–somnolence, agitation, tremor, nausea, diarrhea, dry mouth, vomiting, asthenia, abnormal ejaculation, sweating; **OCD**–insomnia, dizziness, constipation, nausea, asthenia, abnormal ejaculation, impotence; **panic disorder**–somnolence, *insomnia, nausea;* **social anxiety disorder**–somnolence, *insomnia, tremor,* anxiety, dizziness, nausea, vomiting, flatulence, asthenia, abnormal ejaculation, sweating, libido decreased; **generalized anxiety disorder**–somnolence, dizziness, nausea, asthenia, abnormal ejaculation, sweating.

The following adverse events occurred in 6-week placebo-controlled trials of similar design at a frequency of 1% or more, in patients dosed (20 to 50 mg/day) for the treatment of depression: headache, asthenia, palpitation; *vasodilation; sweating, rash; nausea, dry mouth, constipation, diarrhea, decreased appetite, flatulence, oropharynx* disorder, dyspepsia; myopathy, myalgia, myasthenia; somnolence, dizziness, insomnia, tremor, nervousness, anxiety, paresthesia, libido decreased, drugged feeling, confusion; yawn; blurred vision, taste perversion; ejaculatory disturbance, other male genital disorders, urinary frequency, urination disorder, female genital disorders.

The following adverse events occurred at a frequency of 2% or more among OCD patients on *Paxil* who participated *in placebo-controlled trials of 12 weeks duration in which patients were dosed in a range of 20 to 60 mg/* day or among patients with panic disorder on *Paxil* who participated in placebo-controlled trials of 10 to 12 weeks duration in which patients were dosed in a range of 10 to 60 mg/day or among patients with social anxiety disorder on *Paxil* who participated in placebo-controlled trials of 12 weeks duration in which patients were dosed in a range of 20 to 50 mg/day: asthenia, abdominal pain, chest pain, back pain, chills, trauma; vasodilation, palpitation; *sweating, rash; nausea, dry mouth, constipation, diarrhea, decreased appetite, dyspepsia, flatulence, increased* appetite, vomiting; myalgia; insomnia, somnolence, dizziness, tremor, nervousness, libido decreased, agitation, anxiety, abnormal dreams, concentration impaired, depersonalization, myoclonus, amnesia, rhinitis, pharyngitis, yawn; abnormal vision, taste perversion; abnormal ejaculation, dysmenorrhea, female genital disorder, impotence, urinary frequency, urination impaired, urinary tract infection.

The following adverse events occurred at a frequency of 2% or more among GAD patients on Paxil who participated in placebo-controlled trials of 8 weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day; asthenia, headache, infection, vasodilation, sweating, nausea, dry mouth, constipation, diarrhea, decreased appetite, vomiting, insomnia, somnolence, dizziness, tremor, nervousness, libido decreased, respiratory disorder, sinusitis, yawn, abnormal vision, abnormal ejaculation, female genital disorder, impotence.

Studies in depression show a clear dose dependency for some of the more common adverse events associated with *Paxil* use. There was evidence of adaptation to some adverse events with continued *Paxil* therapy (e.g., nausea and dizziness). Significant weight loss may be an undesirable result of *Paxil* treatment for some patients but, on average, patients in controlled trials had minimal (about 1 lb) loss. In placebo-controlled clinical trials, *Paxil*-treated patients exhibited abnormal values on liver function tests no more frequently than placebo-treated patients.

In placebo-controlled clinical trials involving more than 2,500 patients with depression, OCD, panic disorder, social anxiety disorder or generalized anxiety disorder, the following incidences of untoward sexual experiences for patients receiving *Paxil* were reported, varying with the disease state: In males: decreased libido (6% to 15%), ejaculatory disturbance, mostly delayed ejaculation (13% to 28%), impotence (2% to 8%). In females: decreased libido (0% to 9%), orgasmic disturbance (2% to 9%). The reported incidence of each of these adverse events was <5% among male and female patients receiving placebo.

Other Events Observed During the Premarketing Evaluation of *Paxil:* During premarketing assessment in depression multiple doses of *Paxil* were administered to 6,145 patients in phase 2 and 3 studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder and generalized anxiety disorder, 542, 469, 522 and 735 patients, respectively, received multiple doses of *Paxil*. The following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent"= 1/100 to 1/1000 patients; "rare" = less than 1/1000 patients. Events are classified within body system categories and enumerated in order of decreasing frequency using the above definitions. It is important to emphasize that although the events occurred during *Paxil* treatment, they were not necessarily caused by it.

Body as a Whole: *frequent:* chills, malaise; *infrequent:* allergic reaction, face edema, moniliasis, neck pain; *rare:* adrenergic syndrome, cellulitis, neck rigidity, pelvic pain, peritonitis, ulcer. **Cardiovascular System:** *frequent:* hypertension, tachycardia; *infrequent:* bradycardia, hematoma, hypotension, migraine, syncope; *rare:* angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles. **Digestive System:** *infrequent:* bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; *rare:* aphthous stomatitis, bloody diarrhea, bulimia, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries. **Endocrine System:** *rare:* diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis. **Hemic and Lymphatic Systems:** *infrequent:* anemia, eosinophilia, leukocytosis, leukopenia, lymphadenopathy, purpura; *rare:* abnormal erythrocytes, basophilia, bleeding time increased, hypochromic anemia, iron deficiency anemia, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia, thrombocytopenia. **Metabolic and Nutritional:** *frequent:* weight gain, weight loss; *infrequent:* alkaline phosphatase increased, edema, peripheral edema, SGOT increased, SGPT increased, thirst; *rare:* bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased; **Musculoskeletal System:** *frequent:* arthralgia; *infrequent:* arthritis, arthrosis; *rare:* bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany. **Nervous System:** *frequent:* emotional lability, vertigo; *infrequent:* abnormal thinking, alcohol abuse, ataxia, delirium, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction, psychosis; *rare:* abnormal gait, akinesia, antisocial reaction, aphasia, choreoathetosis, circumoral paresthesias, convulsion, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome. **Respiratory System:** *infrequent:* asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, voice alteration. **Skin and Appendages:** *frequent:* pruritus; *infrequent:* acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, furunculosis, herpes simplex, maculopapular rash, photosensitivity, urticaria; *rare:* angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, herpes zoster, hirsutism, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash. **Special Senses:** *frequent:* tinnitus; *infrequent:* abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, photophobia; *rare:* amblyopia, anisocoria, *blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma,* hyperacusis, keratoconjunctivitis, night blindness, otitis externa, parosmia, ptosis, retinal hemorrhage, taste loss, visual field defect. **Urogenital System:** *infrequent:* abortion, amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal moniliasis, vaginitis; *rare:* breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic *breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, pyuria, urethritis,* uterine spasm, urolith, vaginal hemorrhage.

Postmarketing Reports

Voluntary reports of adverse events that have been received since market introduction and not listed above that may have no causal relationship with *Paxil* include–acute pancreatitis, elevated liver function tests (the most *severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver* dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea, neuroleptic malignant syndrome-like events; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis (which has been associated with concomitant use of pimozide), tremor and trismus; serotonin syndrome, *associated in some cases with concomitant use of serotonergic drugs and with drugs which may have impaired Paxil* metabolism (symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia and tremor), status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, and events related to impaired hema*topoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia and agranulocytosis).* There have been spontaneous reports that discontinuation (particularly when abrupt) may lead to symptoms such as dizziness, sensory disturbances, agitation or anxiety, nausea and sweating; these events are generally self-limiting. There has been a report of an elevated phenytoin level after 4 weeks of *Paxil* and phenytoin co-administration, and a report of severe hypotension when *Paxil* was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: *Paxil* is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of *Paxil* misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

BRS–PX:L20

NEW: 1ST AND ONLY SSRI FDA-APPROVED FOR GAD

Overpowered by *ANXIETY*

Empowered by *Paxil*

Generalized anxiety disorder (GAD) patients may suffer for up to **10 years** before diagnosis and treatment,[2] often believing their anxiousness is a part of their personality. With *Paxil*, the **first and only** SSRI FDA-approved for generalized anxiety,[3] they can now find help...and hope.

Most common adverse events (incidence of 5% or greater and incidence for *Paxil* at least twice that for placebo) in depression, OCD, panic disorder, social anxiety disorder or GAD studies include asthenia, infection, sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, dizziness, insomnia, libido decreased, tremor, nervousness, yawn, abnormal ejaculation, female genital disorders and impotence. Concomitant use of *Paxil* in patients taking monoamine oxidase inhibitors (MAOIs) or thioridazine is contraindicated.

VISIT www.paxil.com

Please see brief summary of prescribing information on adjacent page.

ONCE-DAILY
PAXIL
PAROXETINE HCl

The **anxiolytic** antidepressant

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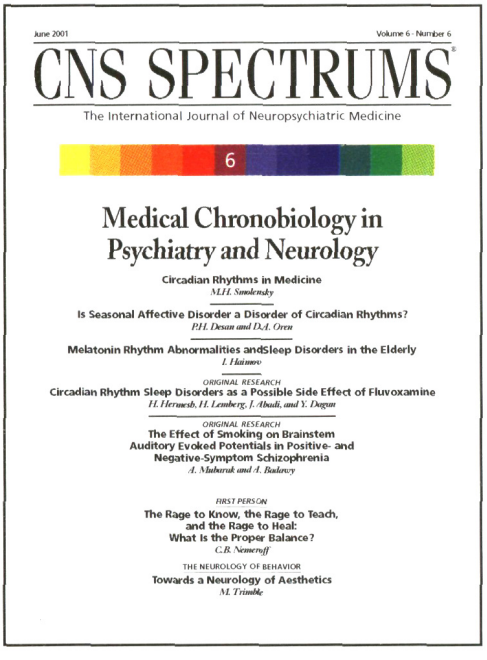

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ALL AROUND SUCCESS

Now all the benefits of REMINYL can help patients with mild to moderate Alzheimer's disease (AD).[1-4]

The most frequent adverse events that occurred with REMINYL were nausea, vomiting, diarrhea, anorexia, and weight loss.

Available in 4-mg, 8-mg, and 12-mg tablets.

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ALL AROUND BENEFITS IN AD

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galantamine HBr Tablets

References: 1. Tariot PN et al. *Neurology*. 2000;54:2269-2276. 2. Raskind MA et al. *Neurology*. 2000;54:2261-2268. 3. Wilcock GK et al. *BMJ*. 2000;321:1-7. 4. Data on file, Janssen.

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Reminyl®
galantamine HBr Tablets

Rx only

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

INDICATION
REMINYL® (galantamine hydrobromide) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS
REMINYL® is contraindicated in patients with known hypersensitivity to galantamine hydrobromide or to any excipients used in the formulation.

WARNINGS
Anesthesia: Galantamine is likely to exaggerate the neuromuscular blockade effects of succinylcholine-type and similar neuromuscular blocking agents during anesthesia.

Cardiovascular Conditions: Cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and AV block. These actions may be particularly important to patients with supraventricular cardiac conduction disorders or to patients taking other drugs concomitantly that significantly slow heart rate. Bradycardia and all types of heart block have been reported in patients both with and without known underlying cardiac conduction abnormalities. Therefore all patients should be considered at risk for adverse effects on cardiac conduction. In randomized controlled trials, bradycardia was reported more frequently in galantamine-treated patients than in placebo-treated patients. No increased incidence of heart block was observed at the recommended doses. Patients treated with galantamine up to 24 mg/day using the recommended dosing schedule showed a dose-related increase in risk of syncope.

Gastrointestinal Conditions: Patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g., those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). REMINYL® has been shown to produce nausea, vomiting, diarrhea, anorexia, and weight loss. (See **ADVERSE REACTIONS**)

Genitourinary: Cholinomimetics may cause bladder outflow obstruction.

Neurological Conditions: Seizures: Cholinesterase inhibitors are believed to have some potential to cause generalized convulsions. In clinical trials, there was no increase in the incidence of convulsions with REMINYL® compared to placebo.

Pulmonary Conditions: Galantamine should be prescribed with care to patients with a history of severe asthma or obstructive pulmonary disease.

PRECAUTIONS
Information for Patients and Caregivers: The recommended administration is twice per day, preferably with morning and evening meal. Dose increases should follow minimum of four weeks at prior dose. Following the recommended dosage and administration can minimize the most frequent adverse events associated with use of the drug. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Special Populations

Hepatic Impairment: In patients with moderately impaired hepatic function, dose titration should proceed cautiously (See **CLINICAL PHARMACOLOGY** in full prescribing information and **DOSAGE AND ADMINISTRATION**). The use of REMINYL® in patients with severe hepatic impairment is not recommended.

Renal Impairment: In patients with moderately impaired renal function, dose titration should proceed cautiously (See **CLINICAL PHARMACOLOGY** in full prescribing information and **DOSAGE AND ADMINISTRATION**). In patients with severely impaired renal function (CL_{cr} < 9 ml/min) the use of REMINYL® is not recommended.

Drug-Drug Interactions

Use with Anticholinergics: Galantamine has the potential to interfere with the activity of anticholinergic medications.

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

A) Effect of Other Drugs on Galantamine: *In vitro* - CYP3A4 and CYP2D6 were the major enzymes involved in the metabolism of galantamine. CYP3A4 mediated the formation of galantamine-N-oxide, whereas CYP2D6 was involved in the formation of O-desmethyl-galantamine. *In vivo* - Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the PK of galantamine. Ketoconazole increased the AUC of galantamine by 30%. Erythromycin affected the AUC of galantamine minimally (10% increase). Paroxetine increased the oral bioavailability of galantamine by about 40%.

B) Effect of Galantamine on Other Drugs: *In vitro* Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. *In vivo* - The protein binding of warfarin was unaffected by galantamine. Galantamine at 24 mg/day had no effect on the steady-state pharmacokinetics of digoxin (0.375 once daily) when they were coadministered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia.

Carcinogenesis, Mutagenesis and Impairment of Fertility: In a 24-month oral carcinogenicity study in rats, a trend for an increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times on an exposure [AUC] basis and 30 mg/kg/day (12 times MRHD on a mg/m² basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m² basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m² and AUC basis). Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m² basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m² basis).

Pregnancy Category B: In a study in which rats were dosed from day 14 (females) or day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis. There are no adequate and well-controlled studies of REMINYL® (galantamine hydrobromide) in pregnant women. REMINYL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether galantamine is excreted in human breast milk. REMINYL® has no indication for use in nursing mothers.

Pediatric Use: There are no adequate and well-controlled trials documenting the safety and efficacy of galantamine in any illness occurring in children. Therefore, use of REMINYL® in children is not recommended.

ADVERSE REACTIONS
Adverse Events Leading to Discontinuation: In two large scale, placebo-controlled trials of 6 months duration, in which patients were titrated weekly from 8 to 16 to 24, and to 32 mg/day, the risk of discontinuation because of an adverse event in the galantamine group exceeded that in the placebo group by about threefold. In contrast, in a 5-month trial with escalation of the dose by 8 mg/day every 4 weeks, the overall risk of discontinuation because of an adverse event was 7%, 7%, and 10% for the placebo, galantamine 16 mg/day, and galantamine 24 mg/day groups, respectively, with gastrointestinal adverse effects (nausea, vomiting and anorexia) the principle reason for discontinuing galantamine.

Adverse Events Reported in Controlled Trials: The majority of reported adverse events occurred during the dose-escalation period of the controlled trials. In those patients who experience the most frequent adverse event, nausea, the median duration of the nausea was 5 to 7 days.

Administration of REMINYL® with food, the use of anti-emetic medication, and ensuring adequate fluid intake may reduce the impact of these events.

The most frequent adverse events, those occurring at a frequency of at least 5% and at least twice the rate on placebo with the recommended maintenance dose of either 16 or 24 mg/day of REMINYL® under conditions of every 4 week dose-escalation, were primarily gastrointestinal and tended to be less frequent with the 16 mg/day recommended initial maintenance dose. They included nausea (5%, 13% and 17%), vomiting (1%, 6% and 10%), diarrhea (6%, 12% and 6%), anorexia (3%, 7% and 9%) and weight decrease (1%, 5% and 5%) for placebo, 16-mg/day and 24-mg/day treatment groups respectively.

The most common adverse events (adverse events occurring with an incidence of 2% with REMINYL® treatment and in which the incidence was greater than with placebo treatment) for patients in controlled trials who were treated with 16 or 24 mg/day of REMINYL® were: fatigue 5%, syncope 2%, dizziness 9%, headache 8%, tremor 3%, nausea 24%, vomiting 13%, diarrhea 9%, abdominal pain 5%, dyspepsia 5%, bradycardia 2%, weight decrease 7%, anorexia 9%, depression 7%, insomnia 5%, somnolence 4%, anemia 3%, rhinitis 4%, urinary tract infection 8% and hematuria 3%.

Adverse events occurring with an incidence of at least 2% in placebo-treated patients that was either equal to or greater than with REMINYL® treatment were constipation, agitation, confusion, anxiety, hallucination, injury, back pain, peripheral edema, asthenia, chest pain, urinary incontinence, upper respiratory tract infection, bronchitis, coughing, hypertension, fall, and purpura.

There were no important differences in adverse event rates related to dose or sex. There were too few non-Caucasian patients to assess the effects of race on adverse event rates.

No clinically relevant abnormalities in laboratory values were observed.

Other Adverse Events Observed During Clinical Trials: The incidence of all adverse events occurring in approximately 0.1% of the patients during clinical trials, except for those adverse events already listed elsewhere in labeling, are defined as: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients; and rare adverse events - those occurring in fewer than 1/1000 patients. **Body As a Whole – General Disorders:** *Frequent:* chest pain; **Cardiovascular System Disorders:** *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure; **Central & Peripheral Nervous System Disorders:** *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia; **Gastrointestinal System Disorders:** *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *rare:* esophageal perforation; **Heart Rate & Rhythm Disorders:** *Infrequent:* AV block, palpitation, atrial fibrillation, QT prolonged, bundle branch block, supraventricular tachycardia, T wave inversion, ventricular tachycardia; **Metabolic & Nutritional Disorders:** *Infrequent:* hyperglycemia, alkaline phosphatase increased; **Platelet, Bleeding & Clotting Disorders:** *Infrequent:* purpura, epistaxis, thrombocytopenia; **Psychiatric Disorders:** *Infrequent:* apathy, paroniria, paranoid reaction, libido increased, delirium; **Urinary System Disorders:** *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi.

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. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics.

DOSAGE AND ADMINISTRATION
The dosage of REMINYL® shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day given in a BID regimen. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL® might provide additional benefit for some patients. The recommended starting dose of REMINYL® is 4 mg twice a day (8 mg/day). After a minimum of 4 weeks of treatment, if this dose is well tolerated, the dose should be increased to 8 mg twice a day (16 mg/day). A further increase to 12 mg twice a day (24 mg/day) should be attempted only after a minimum of 4 weeks at the previous dose. REMINYL® should be administered twice a day, preferably with morning and evening meals. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose.

Doses in Special Populations: Galantamine plasma concentrations may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), the dose should generally not exceed 16 mg/day. The use of REMINYL® in patients with severe hepatic impairment (Child-Pugh score of 10-15) is not recommended. For patients with moderate renal impairment the dose should generally not exceed 16 mg/day. In patients with severe renal impairment (creatinine clearance <9 ml/min), the use of REMINYL® is not recommended.

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