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CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

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Epilepsy: Diagnosis and Treatment in the 21st Century

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ORIGINAL RESEARCH

Reproductive Dysfunction in Women With Epilepsy: Antiepileptic Drug Effects on Sex-Steroid Hormones

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ORIGINAL RESEARCH

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CNS Spectrums is indexed by EMBASE/Excerpta Medica, DIALOG, SilverPlatter, OVID, and Lexis-Nexis, and is the official journal of the International Neuropsychiatric Assoc.

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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

October

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	2	3	4 (–6) International Society for the Study of Personality Disorders: 7th International Congress, New York, NY *contact:* Tel: 212-305-3334 Fax: 212-781-6047	5 (–7) 2nd Congress of the Hellenic Stroke Society: Athens, Greece *contact:* Tel: 30-31-260-645 Fax: 30-31-260-645 nicart@med.auth.gr	6
7	8 *Columbus Day—USA*	9	10 (–13) Mental and Behavioral Dysfunction in Movement Disorders: Montreal, Canada *contact:* Tel: 514-848-1133 Fax: 514-288-6469 bedard.marc-andre@uquam.ca	11 (–13) 1st Canadian Colloquium on Dementia: Toronto, Canada *contact:* Tel: 416-340-5304 Fax: 416-340-4198 rkeren@home.com	12 Johns Hopkins: Neuroradiology Review With Case Reviews, Baltimore, MD *contact:* Tel: 410-955-2959 Fax: 410-955-0807 cmenet@jhmi.edu	13 (–17) European College of Neuropsychopharmacology: 14th Congress, Istanbul, Turkey *contact:* Tel: 31-30-253-8567 Fax: 31-30-253-8568
14	15	16	17 The Royal College of Pathologists: What's New in Pediatric Neuropathology, London, UK *contact:* Tel: 2-74-516-700 Fax: 2-74-516-701 info@rcpath.org	18	19	20
21 (–26) World Conference Sleep Odyssey 2001: Punta del Este, Uruguay *contact:* Tel: 59-80-92-43-414 x3409 Fax: 59-82-92-48-784 sleep2001@fmed.edu.uy	22	23	24	25 (–27) Neuromuscular Disorders in Pediatrics: St. Louis, MO *contact:* Tel: 800-553-2712 Fax: 314-776-4395 cme@slu.edu	26	27 New York University School of Medicine: Review of Practice Guidelines for Treatment of Psychiatric Disorders, New York, NY *contact:* www.med.nyu.edu/cme/
28	29	30	31 **November *CNS* closes & ships to printer**	37th Annual Turkish Neurological Congress: Antalya, Turkey **(Oct 31–Nov 4)** *contact:* Tel: 90-46-23-258-309 Fax: 90-46-23-269-192 mozmenoglu@usa.net	Harry Benjamin International Gender Dysphoria Association 17th Symposium, Galveston, TX **(Oct 31–Nov 4)** *contact:* Tel: 612-625-1500 Fax: 612-626-8311	

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60-Day Planner

MEETINGS DEADLINES REMINDERS

November

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1	*2 (–4)* Baylor College of Medicine: Current Neurology, Houston, TX *contact:* Tel: 713-798-4941 Fax: 713-798-7955 cme@bcm.tmc.edu	*3*
4	*5*	*6*	*7*	*8 (–9)* 2nd Neurobiology of Aging Conference: San Diego, CA *contact:* Tel: 441-865-794-727 Fax: 441-865-794-695 enquiries.oxconf@pop3.hiway.co.uk	*9* Neuro-Psychiatry Update: Los Angeles,CA *contact:* Tel: 617-572-3597 Fax: 617-859-4354 npupdates@hhcc.com	*10 (–15)* 31st Annual Meeting of the Society for Neuroscience: San Diego, CA *contact:* Tel: 202-462-6688 info@sfn.org
11 2nd World Conference of Chinese Neurologists: Hong Kong **(Nov 10–11)** *contact:* Tel: 852-2527-8898 Fax: 852-2866-7530 cosfmshk@netvigator.com	*12 (–15)* Basic Neuroendoscopy Course: Tuttlingen, Germany *contact:* Tel: 497-461-951-015 Fax: 497-461-952-050	*13*	*14*	*15 (–18)* 6th Annual Meeting of Neuro-Oncology: Washington, DC *contact:* Tel: 713-792-2222 Fax: 713-794-1724 meetings@mdaisd1.mdacc.tmc.edu	*16*	*17 (–19)* World Federation of Neurosurgical Societies: Post Graduate Course, Madras, India *contact:* Tel: 91-444-364-150 Fax: 91-444-335-050 kganap@vsnl.com
18	*19*	*20*	*21*	*22* *Thanksgiving—USA* 7th Mediterranean Epilepsy Conference: Athens, Greece **(Nov 22–25)** *contact:* Tel: 30-16-889-100 Fax: 30-16-844-777 congress@cnc.gr	*23*	*24*
25	*26*	*27*	*28* **December *CNS* closes & ships to printer**	*29* 23rd Annual Convention of the Philippine Neurological Association: Iloilo City, Philippines **(Nov 28–Dec 1)** *contact:* Tel: 6-327-232-101 secretariat@pna.com.ph	*30 (–Dec 1)* National Neuroscience Conference: New York, NY *contact:* Tel: 212-305-3334 Fax: 212-781-6047 cme@columbia.edu	

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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 the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart attack in patients both with or without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of ARICEPT®. ***Gastrointestinal Conditions:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®. ***Genitourinary:*** Although not observed in clinical trials of ARICEPT®, 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 Event/%Discontinuing	355	350	315
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. 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. Evidence from the controlled trials indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, 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. ARICEPT® should be taken in the evening, just prior to retiring, and may be taken with or without food.

Revised December 2000

Eisai Inc. Teaneck, NJ 07666

Pfizer CNS Pfizer U.S. Pharmaceuticals New York, NY 10017

ARICEPT® is a registered trademark of Eisai Co., Ltd.

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CNS SPECTRUMS

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SEIZURES AND EPILEPSY: CLASSIFICATION AND DIAGNOSIS

page 750

"An important distinction must be made between seizures and epilepsy, which is the underlying condition characterized by recurrent unprovoked seizures. There are several well-recognized epilepsy syndromes, some of which are considered idiopathic, with an underlying presumed genetic etiology. These syndromes tend to be characterized by specific types of seizures, and often by a typical pattern on electroencephalography... The symptomatic epilepsies have an underlying structural or metabolic cause. Review of these common structural etiologies and appropriate diagnostic evaluations are important not only for the identification of potentially dangerous conditions, but also because curative epilepsy surgery is now an option for many patients."

NOVEL ANTIEPILEPTICS FOR THE NEW MILLENNIUM

page 756

"Drug interactions and the effects of systemic disease on AED disposition are complicated, particularly with the older AEDs. Most of these interactions arise from hepatic induction or inhibition, with consequent alteration of drug half-life. In general, drugs that induce hepatic enzymes will increase the metabolism and decrease the serum concentration of other drugs that are hepatically metabolized. Other interactions, such as increased free fraction of drug, occur when highly plasma-bound agents (phenytoin, valproate, tiagabine) are coadministered... Because they neither cause hepatic induction nor are appreciably affected by it, gabapentin and levetiracetam have virtually no drug-drug interactions. Lamotrigine, topiramate, zonisamide, and tiagabine have little or no effect on other drugs, but their levels can be reduced when given with enzyme inducers. It is nearly impossible to know all pharmacokinetic drug-drug interactions, and, therefore, this information must be researched whenever there is a question. Pharmacodynamic interactions may also occur, which will affect drug action and adverse effects, but not plasma levels."

NEUROSURGERY, LENNOX-GASTAUT SYNDROME, AND THE VNS PATIENT REGISTRY

page 766

"Patients with LGS have seizures that are largely resistant to medical therapy. In studies involving older antiepileptic medications, only 6.7% to 13.7% achieve freedom from seizures. Some of the newer antiepileptic medications (lamotrigine, topiramate, and felbamate) have been studied in the treatment of LGS. The rate of seizure freedom for the newer antiseizure agents was not significantly better than that for the older antiepileptic medications. The ketogenic diet is effective in children with refractory epilepsy, including LGS, and may provide complete seizure control in up to 20% to 30% of patients.[9] However, the diet is difficult to maintain and causes metabolic acidosis, recurrent infections, anorexia, and renal stones in up to 5% of patients."

REPRODUCTIVE DYSFUNCTION AND AEDS IN WOMEN

page 771

"Whether infertility is a consequence of the social and psychological disability often accompanying epilepsy, an effect of seizures and epilepsy on physiological systems supporting reproductive health, or an adverse effect of AEDs, has been debated. Most likely, the causes of reduced birth rates are multifactorial. In the past, women with epilepsy may have been at a social disadvantage; however, the marriage rate for women with epilepsy in the United States is now equivalent to that of the general population. Certainly, women with epilepsy may choose not to become parents, perhaps because of concern about the teratogenic risks of AEDs or because they feel seizures may cause too many parenting difficulties."

COGNITIVE DIFFICULTIES IN ABUSED WOMEN

page 787

"Analysis of variance (ANOVA) was used to examine group comparisons among the nonabused (n=22), IPV without PTSD (PTSD-; n=21), and IPV with PTSD (PTSD+; n=20) groups (Table 1) on self-perceived cognitive difficulties and depression. Post-hoc analyses were conducted with the Tukey test, except when the assumption of homogeneity of variance was violated, in which case Tamhane's T2 was used. Pearson product moment correlations were used to examine the relationships between self-perceived cognitive difficulties and measures of psychological functioning, including severity of PTSD symptoms, severity of depressive symptoms, and daily functioning. A hierarchic regression, controlling for the effects of depression, was also performed on the data to examine the predictive power of PTSD severity on CDS scores. To investigate whether the severity of abuse could predict self-perceived cognitive dysfunction, a stepwise regression was performed, with the psychological aggression, physical assault, sexual coercion, and injury subscales of the CTS-2 as the independent variables and the CDS as the dependent variable. PTSD+ and PTSD- group differences in sexual trauma were examined using the χ^2 test, and ANOVA was performed using the same groups to determine differences in nonsexual assaultative and nonassaultative traumas. Two-tailed tests were used throughout, and α values <0.05 were considered statistically significant."

Reference: 1. Pollack MH, Marzol PC. Pharmacotherapeutic options in the treatment of comorbid depression and anxiety. *CNS Spectrums*. December 2000;5:23-30.

ZOLOFT is indicated for the treatment of major depression, panic disorder, PTSD, and obsessions and compulsions in patients with OCD, and can be used in pediatric patients (aged 6 to 17 years) with OCD. The most common side effects in adults with depression and other premarketing controlled trials, OCD, panic disorder, or PTSD include nausea, insomnia, diarrhea, dry mouth, ejaculation failure (primarily ejaculatory delay), somnolence, fatigue, tremor, dyspepsia, libido decreased, increased sweating, anorexia, and agitation. In pediatric patients, the overall profile of adverse events was similar to that of adults. However, the following events were also reported: hyperkinesia, twitching, fever, malaise, purpura, weight decrease, concentration impaired, manic reaction, emotional lability, thinking abnormal, and epistaxis. ZOLOFT is available in 25 mg, 50 mg, and 100 mg tablets.

BRIEF SUMMARY. Consult the package insert for complete prescribing information.
CONTRAINDICATIONS: Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated. **WARNINGS: Cases of serious sometimes fatal reactions have been reported in patients receiving ZOLOFT in combination with an MAOI. ZOLOFT should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI. PRECAUTIONS: General—Activation of Mania/Hypomania** – During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT-treated patients. **Weight Loss** – Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss. **Seizure** – ZOLOFT has not been evaluated in patients with a seizure disorder. ZOLOFT should be introduced with care in patients with a seizure disorder. **Suicide** – The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Because of the well-established comorbidity between OCD and depression, panic disorder and depression, and PTSD and depression, the same precautions observed when treating patients with depression should be observed when treating patients with OCD, panic disorder, or PTSD. **Weak Uricosuric Effect** – ZOLOFT is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown. **Use in Patients with Concomitant Illness** – Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Use cautiously in patients with diseases or conditions that could affect metabolism or hemodynamic responses. ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. In patients with chronic mild liver impairment, sertraline clearance was reduced, thus increasing AUC, C_{max}, and elimination half-life. Effects in patients with moderate and severe hepatic impairment have not been studied. Approach the use of sertraline with caution in patients with liver disease, and use a lower or less frequent dose in patients with liver impairment. Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. A clinical study has indicated that renal disease does not affect sertraline pharmacokinetics and protein binding. Therefore, no dosage adjustment is needed in patients with renal impairment. **Interference with Cognitive and Motor Performance** – In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. **Hyponatremia** – Several cases of reversible hyponatremia have been reported, mostly in elderly individuals with some taking diuretics or who were otherwise volume depleted. **Platelet Function** – There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking ZOLOFT. While there have been reports of abnormal bleeding or purpura in several patients taking ZOLOFT, it is unclear whether ZOLOFT had a causative role. ***Information for Patients:*** Physicians are advised to discuss the following issues with patients for whom they prescribe ZOLOFT: Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Therefore, patients should be told that until they learn how they respond to ZOLOFT they should be careful doing activities when they need to be alert, such as driving a car or operating machinery. Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol is not advised. Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breastfeeding an infant. ***Drug Interactions:*** **Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins** – Adverse effects may result from displacement of protein-bound ZOLOFT by other tightly bound drugs, eg, warfarin, digitoxin. Prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped. **Cimetidine** – When administering ZOLOFT with cimetidine, dosage adjustment after the starting dose of 50 mg should be guided by clinical effect. **CNS Active Drugs** – Concomitant use of ZOLOFT with diazepam or desmethyldiazepam may require dosage adjustment. Even though lithium levels were not altered in clinical trials, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose. The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Caution is advised if the concomitant use of ZOLOFT and such drugs is required. There is limited controlled experience regarding the optimal timing of switching from other antidepressants to ZOLOFT. Caution should be exercised when switching, particularly from long-acting agents. The duration of an appropriate washout period which should intervene before switching from one selective serotonin reuptake inhibitor (SSRI) to another has not been established. **Drugs Metabolized by P450 3A4** – In two separate *in vivo* interaction studies, sertraline was coadministered with the cytochrome P450 3A4 substrates, terfenadine or carbamazepine, under steady-state conditions. The results of these studies demonstrated that sertraline coadministration did not increase plasma concentrations of terfenadine or carbamazepine. These data suggest that sertraline's extent of inhibition of P450 3A4 activity is not likely to be of clinical significance. **Drugs Metabolized by P450 2D6** – Many antidepressants, eg, the SSRIs, including sertraline, and most tricyclic antidepressants inhibit the biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase), and, thus, may increase the plasma concentrations of coadministered drugs that are metabolized by P450 2D6. This potential interaction is of greatest concern in those drugs metabolized primarily by 2D6 and which have a narrow therapeutic index, eg, the tricyclic antidepressants (TCAs) and the Type 1C antiarrhythmics propafenone and flecainide. The extent to which this interaction is an important clinical problem depends on the extent of the inhibition of P450 2D6 by the antidepressant and the therapeutic index of the coadministered drug. Antidepressants vary in their extent of clinically important 2D6 inhibition; sertraline at lower doses has a less prominent inhibitory effect on 2D6 than some others in the class. Nevertheless, even sertraline has the potential for clinically important 2D6 inhibition. Consequently, concomitant use of a drug metabolized by P450 2D6 with ZOLOFT may require lower doses than usually prescribed for the other drug. Whenever ZOLOFT is withdrawn from co-therapy, an increased dose of the coadministered drug may be required. **Sumatriptan** – Rare reports describe weakness, hyperreflexia, and incoordination following combined SSRI-sumatriptan treatment. Combined therapy warrants appropriate patient observation. **TCAs** – Caution is indicated in the coadministration of TCAs with ZOLOFT, because sertraline may inhibit TCA metabolism. The extent to which SSRI-TCA interactions may pose clinical problems depends on the degree of inhibition and the pharmacokinetics of the SSRI involved. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is co-administered with ZOLOFT. **Hypoglycemic Drugs** – In a placebo-controlled trial in normal volunteers, concomitant use of ZOLOFT and tolbutamide caused a decrease in the clearance of tolbutamide, which may have been due to a change in the metabolism of the drug. The clinical significance of this is unknown. **Atenolol** – ZOLOFT (100 mg) administered to 10 healthy males had no effect on the beta-adrenergic blocking ability of atenolol. **Digoxin** – In another study, administration of ZOLOFT for 17 days (including 200 mg/day for the last 10 days) did not change serum digoxin levels or digoxin renal clearance. **Microsomal Enzyme Induction** – ZOLOFT was shown to induce hepatic microsomal enzymes, as determined by a decrease in antipyrine half-life. This small change reflects a clinically insignificant change in hepatic metabolism. **Electroconvulsive Therapy (ECT)** – There are no clinical studies establishing the risks or benefits of the combined use of ECT and ZOLOFT. **Alcohol** – Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in clinical studies, the concomitant use of ZOLOFT and alcohol is not recommended. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies carried out in mice and rats showed a dose-related increase of liver adenomas in male mice receiving sertraline at 10-40 mg/kg (0.25 - 1.0 times the MRHD on a mg/m² basis). No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg, this effect was not clearly drug related. Sertraline had no genotoxic effects, with or without metabolic activation, based on laboratory assays. A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (4 times the maximum human dose on a mg/m² basis). ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. ZOLOFT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** – The effect of ZOLOFT on labor and delivery in humans is unknown. **Nursing Mothers** – *It is not known whether sertraline or its metabolites are excreted in human milk.* Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman. ***Pediatric Use*** – *In pediatric patients aged 6 to 17 years, drug exposure was generally similar to that of adults, when plasma concentrations were adjusted for weight. The effectiveness of ZOLOFT in pediatric patients with depression or panic disorder has not been systematically evaluated. Regular monitoring of weight and growth is recommended. The risks, if any, that may be associated with the extended use of ZOLOFT in children and adolescents with OCD have not been systematically assessed. There are no studies that directly evaluate the effects of long-term use of sertraline on the growth, development, and maturation of children and adolescents. Although there is no affirmative finding for such effects, the potential of sertraline to have adverse effects with chronic use is not known.* **Geriatric Use** – Geriatric studies of ZOLOFT in depression in patients ≥65 years of age revealed no overall differences in pattern of efficacy or adverse reactions relative to younger patients except for urinary tract infection (incidence ≥2% and greater than placebo). As with all medications, greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, ZOLOFT has been associated with cases of clinically significant hyponatremia in elderly patients. **ADVERSE REACTIONS: Incidence in Placebo-Controlled Clinical Trials—Most Common Treatment-Emergent Adverse Events:** The most common adverse events reported in adult patients receiving ZOLOFT (N=2198; N=1877 for placebo) for the treatment of depression/other, OCD, panic disorder, and PTSD combined in controlled trials (incidence 2% or more for ZOLOFT and greater than placebo): **Autonomic Nervous System Disorders** – ejaculatory failure ([primarily ejaculatory delay; denominator used for male patients only] 14% [n=913] vs 1% [n=773]), mouth dry (15% vs 9%), sweating increased (6% vs 2%). **Central & Peripheral Nervous System Disorders** – somnolence (14% vs 7%), dizziness (12% vs 7%), headache (26% vs 24%), paresthesia (3% vs 2%), tremor (8% vs 2%). **Disorders of Skin and Appendages** – (rash 3% vs 2%). **Gastrointestinal Disorders** – anorexia (6% vs 2%), constipation (7% vs 5%), diarrhea/loose stools (21% vs 11%), dyspepsia (8% vs 4%), flatulence (4% vs 3%), nausea (27% vs 13%), vomiting (4% vs 2%). **General** – fatigue (11% vs 7%), hot flushes (2% vs 1%). **Psychiatric Disorders** – agitation (6% vs 4%), anxiety (4% vs 3%), insomnia (22% vs 11%), libido decreased (6% vs 1%), nervousness (6% vs 4%). **Special Senses** – vision abnormal (4% vs 2%). ***Adverse Events in Pediatric Patients:*** In pediatric patients (n=187), the overall profile was similar to that of adults. However, the following events were also reported (incidence of ≥2% and at least twice that of placebo): hyperkinesia, twitching, fever, malaise, purpura, weight decrease, concentration impaired, manic reaction, emotional lability, thinking abnormal, and epistaxis. ***Associated With Discontinuation of Treatment:*** The adverse events associated with discontinuation of ZOLOFT treatment (incidence at least twice that for placebo and at least 1% for ZOLOFT) in depression and other premarketing controlled trials are agitation, diarrhea, dry mouth, ejaculation failure (primarily ejaculatory delay), headache, insomnia, nausea, somnolence, and tremor; in OCD are diarrhea, dizziness, ejaculation failure (primarily ejaculatory delay), insomnia, nausea, and somnolence; in panic disorder are agitation, diarrhea, dyspepsia, ejaculation failure (primarily ejaculatory delay), insomnia, nausea, nervousness, and somnolence; and in PTSD are headache and nausea. **Sexual Dysfunction with SSRIs:** Although sexual desire, sexual performance, and sexual satisfaction may change as a manifestation of psychiatric disorders, some evidence suggests that SSRIs may cause untoward sexual experiences. Reliable estimates of such untoward experiences are difficult to obtain, due to physician and patient reluctance; accordingly, product labeling is likely to underestimate their actual incidence. There are no adequate, well-controlled studies of sexual dysfunction with sertraline. Priapism has been reported with all SSRIs. Physicians should routinely inquire about possible sexual side effects in patients taking SSRIs. ***Other Events Observed During the Premarketing Evaluation of ZOLOFT:*** During premarketing assessment, multiple doses of ZOLOFT were administered to approximately 4000 adult subjects. Events are further categorized by body system and listed in order of decreasing frequency. Note: frequent=events occurring in at least 1/100 patients; infrequent=1/1000 patients; rare=less than 1/1000 patients. It is important to emphasize that although the events reported occurred during treatment with ZOLOFT, they were not necessarily caused by it. **Autonomic Nervous System Disorders** – *Frequent:* impotence; *Infrequent:* flushing, increased saliva, cold clammy skin, mydriasis; *Rare:* pallor, glaucoma, priapism, vasodilation. **Body as a Whole – General Disorders** – *Rare:* allergic reaction, allergy. **Cardiovascular** – *Frequent:* palpitations, chest pain; *Infrequent:* hypertension, tachycardia, postural dizziness, postural hypotension, periorbital edema, peripheral edema, hypotension, peripheral ischemia, syncope, edema, dependent edema; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, cerebrovascular disorder. **Central and Peripheral Nervous System Disorders** – *Frequent:* hyperkinia, hypoesthesia; *Infrequent:* twitching, confusion, hyperkinesia, vertigo, ataxia, migraine, abnormal coordination, hyperesthesia, leg cramps, abnormal gait, nystagmus, hypokinesia; *Rare:* dysphonia, coma, dyskinesia, hypotonia, ptosis, choreoathetosis, hyporeflexia. **Disorders of Skin and Appendages** – *Infrequent:* pruritus, acne, urticaria, alopecia, dry skin, erythematous rash, photosensitivity reaction, maculopapular rash; *Rare:* follicular rash, eczema, dermatitis, contact dermatitis, bullous eruption, hypertrichosis, skin discoloration, pustular rash. **Endocrine Disorders** – *Rare:* exophthalmos, gynecomastia. **Gastrointestinal Disorders** – *Frequent:* appetite increased; *Infrequent:* dysphagia, tooth caries aggravated, eructation, esophagitis, gastroenteritis; *Rare:* melena, glossitis, gum hyperplasia, hiccup, stomatitis, tenesmus, colitis, diverticulitis, fecal incontinence, gastritis, rectum hemorrhage, hemorrhagic peptic ulcer, proctitis, ulcerative stomatitis, tongue edema, tongue ulceration. **General** – *Frequent:* back pain, asthenia, malaise, weight increase; *Infrequent:* fever, rigors, generalized edema; *Rare:* face edema, aphthous stomatitis. **Hearing and Vestibular Disorders** – *Rare:* hyperacusis, labyrinthine disorder. **Hematopoietic and Lymphatic** – *Rare:* anemia, anterior chamber eye hemorrhage. **Liver and Biliary System Disorders** – *Rare:* abnormal hepatic function. **Metabolic and Nutritional Disorders** – *Infrequent:* thirst; *Rare:* hypoglycemia, hypoglycemia reaction. **Musculoskeletal System Disorders** – *Frequent:* myalgia; *Infrequent:* arthralgia, dystonia, arthrosis, muscle cramps, muscle weakness. **Psychiatric Disorders** – *Frequent:* yawning, other male sexual dysfunction, other female sexual dysfunction; *Infrequent:* depression, amnesia, paroniria, teeth-grinding, emotional lability, apathy, abnormal dreams, euphoria, paranoid reaction, hallucination, aggressive reaction, aggravated depression, delusions; *Rare:* withdrawal syndrome, suicide ideation, libido increased, somnambulism, illusion. **Reproductive** – *Infrequent:* menstrual disorder, dysmenorrhea, intermenstrual bleeding, vaginal hemorrhage, amenorrhea, leukorrhea; *Rare:* female breast pain, menorrhagia, balanoposthitis, breast enlargement, atrophic vaginitis, acute female mastitis. **Respiratory System Disorders** – *Frequent:* rhinitis; *Infrequent:* coughing, dyspnea, upper respiratory tract infection, epistaxis, bronchospasm, sinusitis; *Rare:* hyperventilation, bradypnea, stridor, apnea, bronchitis, hemoptysis, hypoventilation, laryngismus, laryngitis. **Special Senses** – *Frequent:* tinnitus; *Infrequent:* conjunctivitis, earache, eye pain, abnormal accommodation; *Rare:* xerophthalmia, photophobia, diplopia, abnormal lacrimation, scotoma, visual field defect. **Urinary System Disorders** – *Infrequent:* micturition frequency, polyuria, urinary retention, dysuria, nocturia, urinary incontinence; *Rare:* cystitis, oliguria, pyelonephritis, hematuria, renal pain, strangury. **Laboratory Tests:** Asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%). Hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of treatment and promptly diminished upon drug discontinuation. ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance. The safety profile observed with ZOLOFT treatment in patients with depression, OCD, panic disorder, and PTSD is similar. ***Other Events Observed During the Postmarketing Evaluation of ZOLOFT:*** Reports of adverse events received since market introduction that are not listed above and that may have no causal relationship with ZOLOFT include: acute renal failure, anaphylactoid reaction, angioedema, blindness, optic neuritis, cataract, increased coagulation times, bradycardia, AV block, atrial arrhythmias, QT-interval prolongation, ventricular tachycardia (including torsade de pointes-type arrhythmias), hypothyroidism, agranulocytosis, aplastic anemia and pancytopenia, leukopenia, thrombocytopenia, lupus-like syndrome, serum sickness, hyperglycemia, galactorrhea, hyperprolactinemia, neuroleptic malignant syndrome-like events, extrapyramidal symptoms, oculogyric crisis, serotonin syndrome, psychosis, pulmonary hypertension, severe skin reactions, which potentially can be fatal, such as Stevens-Johnson syndrome, vasculitis, photosensitivity and other severe cutaneous disorders, rare reports of pancreatitis, and liver events — clinical features (which in the majority of cases appeared to be reversible with discontinuation of ZOLOFT) occurring in one or more patients include: elevated enzymes, increased bilirubin, hepatomegaly, hepatitis, jaundice, abdominal pain, vomiting, liver failure and death. **DRUG ABUSE AND DEPENDENCE: Controlled Substance Class** – ZOLOFT is not a controlled substance. Premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. Physicians, however, should carefully evaluate patients for history of drug abuse and observe them for signs of ZOLOFT misuse or abuse. **OVERDOSAGE:** Symptoms of ZOLOFT overdose, alone or in combination with other drugs, included, most commonly, somnolence, vomiting, tachycardia, nausea, dizziness, agitation, and tremor. Other important adverse events included bradycardia, bundle branch block, coma, convulsions, delirium, hallucinations, hypertension, hypotension, manic reaction, pancreatitis, QT-interval prolongation, serotonin syndrome, stupor, and syncope. Reports of death attributed to overdoses of ZOLOFT alone have been extremely rare. Any overdosage should be treated aggressively by ensuring an adequate airway, oxygenation, and ventilation. Gastric lavage with appropriate airway protection, may be indicated. Induction of emesis is not recommended.

Pfizer CNS

Revision 8

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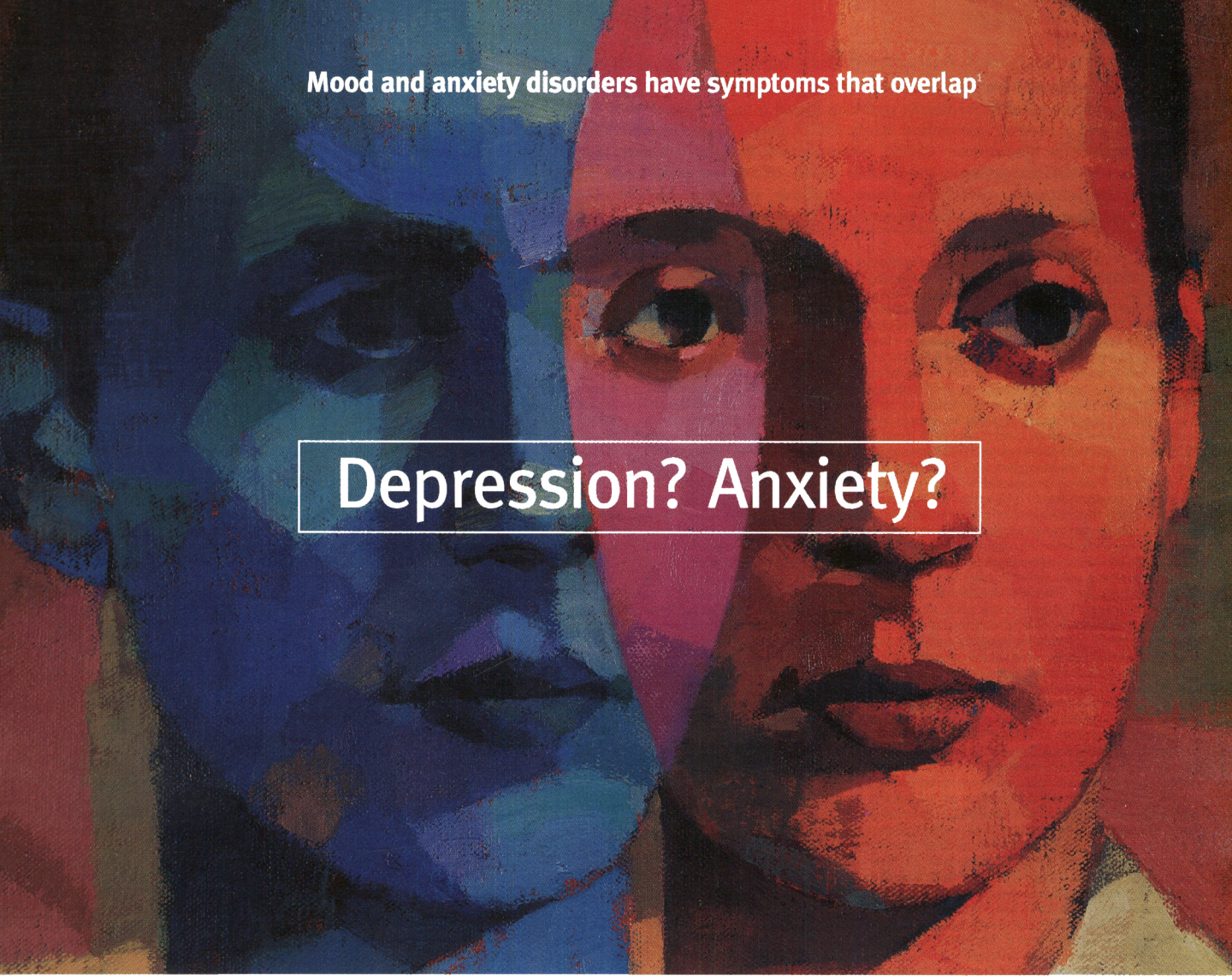

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*The #1 Prescribed SSRI in New Rxs and Total Rxs**

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Major depression	**Panic disorder**	**Obsessive-compulsive disorder (OCD)** **–adult** **–pediatric**	**Posttraumatic stress disorder (PTSD)**

*IMS America National Prescription Audit, May 2001.

ZOLOFT is contraindicated until at least 14 days have passed since discontinuing a monoamine oxidase inhibitor (MAOI) and an MAOI is contraindicated for at least 14 days after discontinuation of ZOLOFT (see WARNINGS in prescribing information).

Please see brief summary of prescribing information on adjacent page.

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Zoloft® (sertraline HCl)

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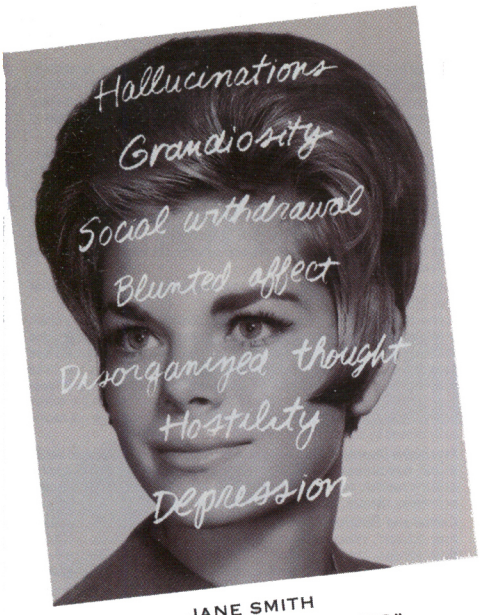

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Please see brief summary of full Prescribing Information on adjacent page.

Reference: 1. IMS Health, NPA Plus, New and Total Prescriptions, 12 months ending November 2000.

*Data on file, 2000. Submitted for publication.

In two 6- to 8-week placebo-controlled trials, spontaneously reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to RISPERDAL therapy include diabetes mellitus aggravated, including diabetic ketoacidosis.

Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12–16 mg/day, well above the recommended dose. Risperidone has not been evaluated in patients with a recent history of myocardial infarction or unstable heart disease.

Percentage of patients experiencing weight gain (≥7% of baseline body weight) in controlled clinical trials was 9% placebo versus 18% risperidone. This difference is statistically significant. Weight gain was dose dependent in short-term clinical trials. Other weight-related adverse events occurring in premarketing studies and listed as infrequent include increased appetite, weight increase, and weight decrease.

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RISPERIDONE

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

INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the management of the manifestations of psychotic disorders.

CONTRAINDICATIONS

RISPERDAL® (risperidone) is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (See DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment and in patients with severe hepatic impairment. A lower starting dose should be used in such patients.

Information for Patients

Physicians are advised to consult full prescribing information to review issues to be discussed with patients for whom they prescribe RISPERDAL®.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists. Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas.

These findings are considered to be prolactin medicated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis.

Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of RISPERDAL® on labor and delivery in humans is unknown.

Nursing Mothers

It is not known whether or not risperidone is excreted in human milk. Women receiving RISPERDAL® should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (See PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (See DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% percent (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included: extrapyramidal symptoms, dizziness, hyperkinesia, somnolence, and nausea.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

The following adverse events occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL® treated patients treated at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials: ***Psychiatric Disorders:*** insomnia, agitation, anxiety, somnolence, aggressive reaction. ***Nervous System:*** extrapyramidal symptoms[1], headache, dizziness. ***Gastrointestinal System:*** constipation, nausea, dyspepsia, vomiting, abdominal pain, saliva increased, toothache. ***Respiratory System:*** rhinitis, coughing, sinusitis, pharyngitis, dyspnea. ***Body as a Whole:*** back pain, chest pain, fever. ***Dermatological:*** rash, dry skin, seborrhea. ***Infections:*** upper respiratory. ***Visual:*** abnormal vision. ***Musculo-Skeletal:*** arthralgia. ***Cardiovascular:*** tachycardia.

[1] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders.

Dose Dependency of Adverse Events:

Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment. These symptoms include: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: A statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies and the following reactions were reported: (Note: frequent adverse events are those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.)

Psychiatric Disorders: *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-intestinal Disorders: *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastro-esophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: *Rare:* bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

For information on symptoms and treatment of overdosage, see full prescribing information.

More detailed professional information is available upon request.

US Patent 4,804,663

7503217

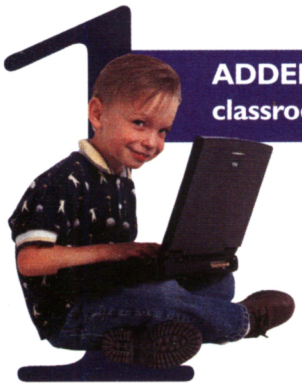
July 1998, May 1999

JANSSEN · PHARMACEUTICA · · RESEARCH FOUNDATION ·

Titusville, NJ 08560

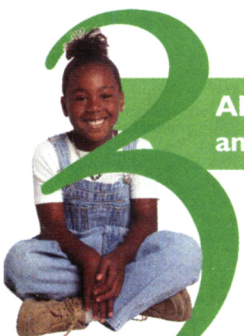
In the medical management of ADHD…

FIVE reasons to *consider* the proven *efficacy*[1,2] of ADDERALL® for the ADHD *patients* in *your* practice...



ADDERALL—Significant improvement across numerous classroom measures compared to placebo ($p<0.0001$)[1]

ADDERALL—Significant improvement in controlling inattentive and overactive behaviors ($p<0.05$)[2]



ADDERALL—Significant improvement in reducing aggressive and defiant behaviors ($p<0.05$)[2]

ADDERALL—Significant number of medication responders ($p<0.01$)[2]

ADDERALL—Significant Clinical Global Impression (CGI) improvement scores ($p<0.05$)[2]

ADDERALL is generally well tolerated. The most frequently reported adverse reactions include anorexia, insomnia, stomach pain, headache, irritability, and weight loss. As with other psychostimulants indicated for ADHD, there is a potential for precipitating motor tics and Tourette's syndrome. In rare cases, psychosis has been reported.

ADDERALL is contraindicated in patients with symptomatic cardiovascular disease, moderate to severe hypertension, or history of drug abuse. Amphetamines may exacerbate symptoms of behavior disturbance and thought disorder in psychotic children. The possibility of growth inhibition warrants monitoring growth during treatment.

ADDERALL should be prescribed only as part of an overall multimodal treatment program for ADHD with close physician supervision.

ADDERALL XR®

5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg & 30 mg TABLETS

(Mixed Salts of a Single-Entity Amphetamine Product)

Dextroamphetamine Sulfate — Amphetamine Sulfate

Dextroamphetamine Saccharate — Amphetamine Aspartate

ADDERALL is a registered trademark of Shire US Inc.

Please see adjacent page for references and full prescribing information.

Shire

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References: 1. Pelham WE, Aronoff HR, Midlam JK, et al. A comparison of Ritalin and Adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. *Pediatrics* [serial online]. 1999;103:e43. Available at: http://www.pediatrics.org/. **2.** Pliszka S, Browne RG, Wynne SK, et al. Comparing Adderall and methylphenidate in ADHD. *J Am Acad Child Adolesc Psychiatry.* 2000; 39(5):619-626.

ADDERALL® XR

5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg & 30 mg TABLETS
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Amphetamine Sulfate
Dextroamphetamine Saccharate Amphetamine Aspartate

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

DESCRIPTION: A single entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and d, l-amphetamine aspartate.

EACH TABLET CONTAINS:	5 mg	7.5 mg	10 mg	12.5 mg	15 mg	20 mg	30 mg
Dextroamphetamine Saccharate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Amphetamine Aspartate	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Dextroamphetamine Sulfate USP	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Amphetamine Sulfate USP	1.25 mg	1.875 mg	2.5 mg	3.125 mg	3.75 mg	5 mg	7.5 mg
Total amphetamine base equivalence	3.13 mg	4.7 mg	6.3 mg	7.8 mg	9.4 mg	12.6 mg	18.8 mg

Inactive Ingredients: sucrose, lactose, corn starch, acacia and magnesium stearate.

Colors: ADDERALL 5 mg, 7.5 mg and 10 mg contain FD & C Blue #1.

ADDERALL 12.5 mg, 15 mg, 20 mg and 30 mg contain FD & C Yellow #6 as a color additive.

CLINICAL PHARMACOLOGY: Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action.

There is neither specific evidence which clearly establishes the mechanism whereby amphetamine produces mental and behavioral effects in children, nor conclusive evidence regarding how these effects relate to the condition of the central nervous system.

INDICATIONS: Attention Deficit Disorder with Hyperactivity: Adderall is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

In Narcolepsy

CONTRAINDICATIONS:
Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.
Agitated states.
Patients with a history of drug abuse.
During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS: Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment.

Usage in Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

PRECAUTIONS: General: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension.

The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Drug Interactions: *Acidifying agents* - Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines.
Urinary acidifying agents -
(ammonium chloride, sodium acid phosphate, etc.) Increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.
Adrenergic blockers -
Adrenergic blockers are inhibited by amphetamines.
Alkalinizing agents -
Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines.
Antidepressants, tricyclic -
Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.
MAO inhibitors -
MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results.
Antihistamines -
Amphetamines may counteract the sedative effect of antihistamines.
Antihypertensives -
Amphetamines may antagonize the hypotensive effects of antihypertensives.
Chlorpromazine -
Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning.
Ethosuximide -
Amphetamines may delay intestinal absorption of ethosuximide.
Haloperidol -
Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.
Lithium carbonate -
The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.
Meperidine -
Amphetamines potentiate the analgesic effect of meperidine.
Methenamine therapy -
Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy.
Norepinephrine -
Amphetamines enhance the adrenergic effect of norepinephrine.
Phenobarbital -
Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.
Phenytoin -
Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.
Propoxyphene -
In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.
Veratrum alkaloids -
Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions:
- Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening.
- Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis: Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of amphetamine, have not been performed.

Pregnancy - Teratogenic Effects: Pregnancy Category C. Amphetamine has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Pediatric Use: Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE.

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics. When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated.

ADVERSE REACTIONS:
Cardiovascular: Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect.

Allergic: Urticaria.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE: Dextroamphetamine sulfate is a Schedule II controlled substance.
Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines.

OVERDOSAGE: Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal.

In rats, the oral LD_{50} of dextroamphetamine sulfate is 96.8 mg/kg.

Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis.

Fatigue and depression usually follow the central stimulation.

Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse.

Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment: Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

DOSAGE AND ADMINISTRATION: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia.
Attention Deficit Disorder with Hyperactivity: Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained.

In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy.

Narcolepsy: Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response.

Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours.

HOW SUPPLIED:
ADDERALL® 5 mg: Blue double-scored tablet, debossed "AD" on one side and "5" on the other side (NDC 58521-031-01)
ADDERALL® 7.5 mg: Blue double-scored tablet, debossed "AD" on one side and "7.5" on the other side (NDC 58521-075-01)
ADDERALL® 10 mg: Blue double-scored tablet, debossed "AD" on one side and "10" on the other side (NDC 58521-032-01)
ADDERALL® 12.5 mg: Orange double-scored tablet, debossed "AD" on one side and "12.5" on the other side (NDC 58521-125-01)
ADDERALL® 15 mg: Orange double-scored tablet, debossed "AD" on one side and "15" on the other side (NDC 58521-150-01)
ADDERALL® 20 mg: Orange double-scored tablet, debossed "AD" on one side and "20" on the other side (NDC 58521-033-01)
ADDERALL® 30 mg: Orange double-scored tablet, debossed "AD" on one side and "30" on the other side (NDC 58521-034-01)

In bottles of 100 tablets.

Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).

Rx only.

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