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In mild to moderate Alzheimer's disease

You see it as maintaining cognitiv

* *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).

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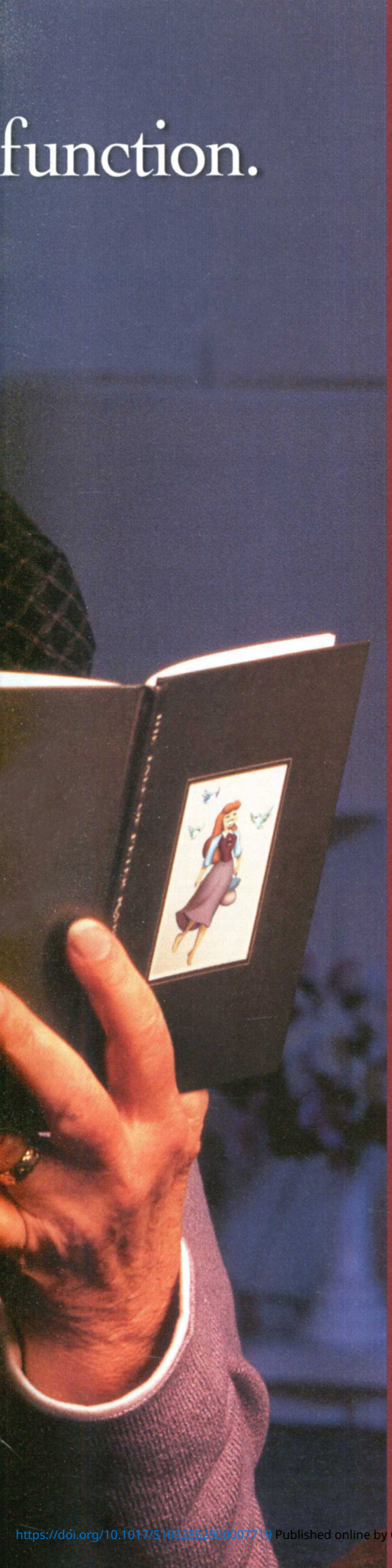

function.

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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ARICEPT® (Donepezil Hydrochloride Tablets)

Brief Summary – see package insert for full prescribing information. **INDICATIONS AND USAGE** ARICEPT® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. **CONTRAINDICATIONS** ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS** ***Anesthesia:*** ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. ***Cardiovascular Conditions:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. Syncopal episodes have been reported in association with the use of ARICEPT®. ***Gastrointestinal Conditions:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®. ***Genitourinary:*** Although not observed in clinical trials of ARICEPT®, cholinomimetics may cause bladder outflow obstruction. ***Neurological Conditions:*** Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease. ***Pulmonary Conditions:*** Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **PRECAUTIONS Drug-Drug Interactions *Drugs Highly Bound to Plasma Proteins:*** Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. ARICEPT® at concentrations of 0.3-10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL), and warfarin (3 µg/mL) to human albumin. Similarly, the binding of ARICEPT® to human albumin was not affected by furosemide, digoxin, and warfarin. ***Effect of ARICEPT® on the Metabolism of Other Drugs:*** No *in vivo* clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50-130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT® has any potential for enzyme induction is not known. ***Effect of Other Drugs on the Metabolism of ARICEPT®:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of these inhibitors is not known. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. ***Use with Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. ***Use with Cholinomimetics and Other Cholinesterase Inhibitors:*** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity studies of donepezil have not been completed. Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis). **Pregnancy *Pregnancy Category C:*** Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m² basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m² basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers. **Pediatric Use** There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children. **ADVERSE REACTIONS Adverse Events Leading to Discontinuation** The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

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

Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®
Patients Randomized	355	350	315
Event/%Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT® The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day. See Table 2 for a comparison of the most common adverse events following one and six week titration regimens.

Table 2. Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks

Adverse Event	Placebo (n=315)	No titration 5 mg/day (n=311)	One-week titration 10 mg/day (n=315)	Six-week titration 10 mg/day (n=269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Adverse Events Reported in Controlled Trials The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

Table 3. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT® (donepezil HCl) and at a Higher Frequency than Placebo-treated Patients

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

Other Adverse Events Observed During Clinical Trials ARICEPT® has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days. Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT®. All adverse events occurring at least twice are included, except for those already listed in Tables 2 or 3, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events* — those occurring in at least 1/100 patients; *infrequent adverse events* — those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States. **Body as a Whole:** *Frequent:* influenza, chest pain, toothache; *Infrequent:* fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness. **Cardiovascular System:** *Frequent:* hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; *Infrequent:* angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis. **Digestive System:** *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. **Endocrine System:** *Infrequent:* diabetes mellitus, goiter. **Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. **Metabolic and Nutritional Disorders:** *Frequent:* dehydration; *Infrequent:* gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. **Musculoskeletal System:** *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation. **Nervous System:** *Frequent:* delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. **Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. **Skin and Appendages:** *Frequent:* pruritus, diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. **Urogenital System:** *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. **Postintroduction Reports** Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash. **OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.** As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature. **DOSAGE AND ADMINISTRATION** The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day. Controlled clinical trials indicated that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. Because steady state is not achieved for 15 days and because the incidence of such effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks. Whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference. ARICEPT® should be taken in the evening, just prior to retiring, and may be taken with or without food.

Revised September 1999

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Pfizer U.S. Pharmaceuticals New York, NY 10017

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CNS SPECTRUMS

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AN IMMUNOLOGIC CONTRIBUTION?

page 17

"Platelet dysfunction and thrombocytopenia rarely occur during clozapine therapy, but constitute an important source of morbidity and mortality if they are not detected and therapy is discontinued. The manufacturer recommends discontinuing clozapine when the platelet count falls below 100,000/μL and resuming therapy when the count returns to within normal range (150,000–450,000/μL). If thrombocytopenia recurs, clozapine should be permanently discontinued.

The authors report a rare case of long-term thrombocytopenia persisting 40 months post-clozapine treatment. In addition, increased in vitro platelet [^{14}C]serotonin release was observed in the presence of the drug, suggesting an immune-related cause for the thrombocytopenia."

IN SEARCH OF A DISTINCTION

page 19

"Autistic disorder and catatonia are neuropsychiatric syndromes defined by impairments in social interaction, communication, and restricted, stereotypical motor routines. Assessments of children with these disorders are typically restricted in scope by the patients' limited ability to comprehend directions. The authors performed systematic assessments of dyskinesias on six prepubertal boys with autistic disorder and mental retardation and on one adolescent male with catatonia to determine if this type of information could be routinely obtained. The boys with autistic disorder had more stereotypies and tics, a greater degree of akathisia and hyperactivity, and more compulsions than the adolescent with catatonia. Catatonia was associated with catalepsy and dystonic postures. The authors conclude that the diagnostic accuracy and specificity of neuropsychiatric syndromes may be enhanced by the systematic assessment of the dyskinesias associated with each condition."

THE ANXIETY-DEPRESSION OVERLAP

page 23

"Historically, anxiety and depression have been considered separate illnesses that were treated with anxiolytics or antidepressants, respectively; however, these two disorders share symptoms that can complicate their differential diagnosis and treatment. In a review of 10 studies of patients with anxiety and seven studies of patients with depression, Wetzler and Katz reported that the disorders coexisted in approximately 50% of patients. Clinically, it is common for a patient with a primary diagnosis of depression to report symptoms of anxiety or a patient with anxiety to experience symptoms of depression. The overlap between these entities has been explained in several ways: depression and anxiety may be distinct entities, may coexist, or may be a separate, mixed disease with symptoms that are below the diagnostic threshold for either disorder alone. The exact nature of the overlap between depression and anxiety remains controversial. Genetic, neurobiologic, and pharmacologic evidence yields conflicting results, depending on the population under study, with some studies suggesting that these conditions are closely related and others emphasizing their discrete nature. For diagnostic purposes, depressive and anxiety disorders are classified as distinct, although frequently comorbid, entities in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*). Mixed anxiety-depressive disorder (MAD) is included as a provisional category in the *DSM-IV-TR*. Regardless of the theoretical basis for the various presentations of these disorders, a substantial overlap exists in their pharmacotherapy."

IDENTIFYING PREDISPOSING FACTORS

page 31

"This article focuses on the clinical onset of obsessive-compulsive disorder (OCD), specifically addressing the age of onset, gradual and acute onset, and whether there are some types of premorbid conditions or a prodromal phase that predispose individuals to the onset of OCD. Clinical and epidemiological studies have come to different conclusions regarding age at onset as well as regarding differences between the sexes. Data gleaned from research to date have demonstrated a relationship between OCD and obsessive-compulsive personality disorder (OCPD), although OCPD does not appear to be the more prevalent personality disorder among patients with OCD. Preliminary research has suggested that Axis I disorders may predispose individuals to OCD onset; however, the significance of this relationship remains to be clarified. Evidence of the association between OCD and subthreshold obsessive-compulsive syndrome suggests that these disorders lie on a continuum of severity, with some cases developing OCD while others do not."

THE QUESTION OF LIFE EVENTS AS TRIGGERS

page 44

"Although many investigations into the onset of obsessive-compulsive disorder (OCD) suggest the occurrence of potential life events as triggering factors, such an association has not been well studied to date. The purpose of the present paper is to review the literature on OCD onset in order to determine whether OCD is triggered by recent life events, what specific events may serve as triggers, and the clinical and research implications of these factors. Overall, the available studies do not consistently support the theory that OCD is triggered by specific antecedent life events. However, there is a body of evidence to support the theory that the specific life events of pregnancy and birth of a child can trigger OCD. This apparent association has led to the investigation of certain neurohormonal factors, including changes in estrogen or oxytocin levels, that may be of etiopathogenetic significance in OCD. Confirming such associations may allow clinicians to provide more targeted preventive and therapeutic interventions."

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Brief Summary
Sonata® (zaleplon) Capsules
See package insert for full prescribing information.
Contraindications: None known.
Warnings: Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including Sonata. Because some of the important adverse effects of Sonata appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly.
A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (eg, aggressiveness and extroversion that seem out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics. it can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation. Following rapid dose decrease or abrupt discontinuation of the use of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see **Drug Abuse and Dependence**). Sonata, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, Sonata should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients receiving Sonata should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (eg, operating machinery or driving a motor vehicle) after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of Sonata. Sonata, as well as other hypnotics, may produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression. Sonata should not be taken with alcohol. Dosage adjustment may be necessary when Sonata is administered with other CNS depressant agents because of the potentially additive effects.
Precautions: GENERAL—*Timing of Drug Administration:* Sonata should be taken immediately before bedtime or after the patient has gone to bed and has experienced difficulty falling asleep. As with all sedative/hypnotics, taking Sonata while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.
Use in the elderly and/or debilitated patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. A dose of 5 mg is recommended for elderly patients to decrease the possibility of side effects. Elderly and/or debilitated patients should be monitored closely.
Use in patients with concomitant illness: Clinical experience with Sonata in patients with concomitant systemic illness is limited. Sonata should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although preliminary studies did not reveal respiratory depressant effects at hypnotic doses of Sonata in normal subjects, caution should be observed if Sonata is prescribed to patients with compromised respiratory function, because sedative/hypnotics have the capacity to depress respiratory drive. Controlled trials of acute administration of Sonata 10 mg in patients with chronic obstructive pulmonary disease or moderate obstructive sleep apnea showed no evidence of alterations in blood gases or apnea/hypopnea index, respectively. However, patients with compromised respiration due to preexisting illness should be monitored carefully. The dose of Sonata should be reduced to 5 mg in patients with mild to moderate hepatic impairment. It is not recommended for use in patients with severe hepatic impairment.
No dose adjustment is necessary in patients with mild to moderate renal impairment. Sonata has not been adequately studied in patients with severe renal impairment.
Use in patients with depression: As with other sedative/hypnotic drugs, Sonata should be administered with caution to patients exhibiting signs or symptoms of depression. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients (see **OVERDOSAGE**); therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.
INFORMATION FOR PATIENTS: Patient information is printed in the complete prescribing information.
LABORATORY TESTS: There are no specific laboratory tests recommended.
DRUG INTERACTIONS: *CNS-active Drugs*—Ethanol: Sonata potentiated the CNS-impairing effects of ethanol. The potentiation resulted from a CNS pharmacodynamic interaction; zaleplon did not affect the pharmacokinetics of ethanol.
Imipramine/Thioridazine: Coadministration of single doses of Sonata 20 mg and imipramine 75 mg or thioridazine 50 mg produced additive effects on decreased alertness and impaired psychomotor performance for 2 to 4 hours after administration. The interaction was pharmacodynamic with no alteration of the pharmacokinetics of either drug.
Paroxetine: Coadministration of a single dose of Sonata 20 mg and paroxetine 20 mg daily for 7 days did not produce any interaction on psychomotor performance. Additionally, paroxetine did not alter the pharmacokinetics of Sonata, reflecting the absence of a role of CYP2D6 in zaleplon's metabolism.
Drugs that Induce CYP3A4—Rifampin: Multiple-dose administration of the potent CYP3A4 inducer rifampin (600 mg every 24 hours, q24h, for 14 days), reduced zaleplon C_{max} and AUC by approximately 80%. The coadministration of a potent CYP3A4 enzyme inducer, although not posing a safety concern, thus could lead to ineffectiveness of zaleplon.
Drugs that Inhibit CYP3A4—The coadministration of a potent, selective CYP3A4 inhibitor is not expected to produce a clinically important pharmacokinetic interaction with zaleplon; however, there are no clinical studies specifically addressing this question.
Drugs that Inhibit Aldehyde Oxidase—Diphenhydramine: Diphenhydramine is reported to be a weak inhibitor of aldehyde oxidase in rat liver. There is no pharmacokinetic interaction between zaleplon and diphenhydramine following the administration of a single dose (10 mg and 50 mg, respectively) of each drug. However, because both of these compounds have CNS effects, an additive pharmacodynamic effect is possible.
Drugs that Inhibit Both Aldehyde Oxidase and CYP3A4—Cimetidine: Cimetidine inhibits both aldehyde oxidase (in vitro) and CYP3A4 (in vitro and in vivo), the primary and secondary enzymes, respectively, responsible for zaleplon metabolism. Concomitant administration of Sonata (10 mg) and cimetidine (800 mg) produced an 85% increase in the mean C_{max} and AUC of zaleplon. An initial dose of 5 mg should be given to patients who are concomitantly being treated with cimetidine.
Drugs Highly Bound to Plasma Protein—Zaleplon is not highly bound to plasma proteins (fraction bound 60%±15%); therefore, the disposition of zaleplon is not expected to be sensitive to alterations in protein binding. In addition, administration of Sonata to a patient taking another drug that is highly protein bound should not cause transient increase in free concentrations of the other drug.
Drugs with a Narrow Therapeutic Index—Digoxin: Sonata (10 mg) did not affect the pharmacokinetic or pharmacodynamic profile of digoxin (0.375 mg q24h for 8 days).
Warfarin: Multiple oral doses of Sonata (20 mg q24h for 13 days) did not affect the pharmacokinetics of warfarin (R+)- or (S-)-enantiomers or the pharmacodynamics (prothrombin time) following a single 25 mg oral dose of warfarin.
Drugs that Alter Renal Excretion—Ibuprofen: There was no apparent pharmacokinetic interaction between zaleplon and ibuprofen following single dose administration (10 mg and 600 mg, respectively) of each drug. This was expected because zaleplon is primarily metabolized, and renal excretion of unchanged zaleplon accounts for less than 1% of the administered dose.
CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY—*Carcinogenesis:* Mice received doses equivalent to 6 - 49 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. There was a significant increase in the incidence of hepatocellular adenomas in female mice in the high dose group. Rats received doses equivalent to 0.5 - 10 times the MRHD. Zaleplon was not carcinogenic in rats.
Mutagenesis: Zaleplon was clastogenic when tested for chromosomal aberrations in the in vitro Chinese hamster ovary cell assay. In the in vitro human lymphocyte assay, zaleplon caused numerical but not structural aberrations, only in the presence of metabolic activation at the highest concentrations tested. Zaleplon was not mutagenic in the Ames bacterial gene mutation assay or the Chinese hamster ovary HGPRT gene mutation assay. Zaleplon was not clastogenic in two in vivo assays, the mouse bone marrow micronucleus assay and the rat bone marrow chromosomal aberration assay, and did not cause DNA damage in the rat hepatocyte unscheduled DNA synthesis assay.
Impairment of Fertility: In a study in rats, mortality and decreased fertility were associated with administration of an oral dose of zaleplon of 100 mg/kg/day to males and females prior to and during mating. Follow-up studies indicated that impaired fertility was due to an effect on the female.
PREGNANCY—*Pregnancy Category C:* Oral administration of up to 100 and 50 mg/kg/day, respectively, to pregnant animals (rats and rabbits) throughout organogenesis produced no evidence of teratogenicity. In rats, pre- and postnatal growth was reduced in the offspring of dams receiving 100 mg/kg/day. This dose was also maternally toxic, as evidenced by clinical signs and decreased maternal body weight gain during gestation. The no-effect dose for rat offspring growth reduction was 10 mg/kg (a dose equivalent to 5 times the MRHD of 20 mg on a mg/m^2 basis). No adverse effects on embryofetal development were observed in rabbits at the doses examined.
In a pre- and postnatal development study in rats, increased stillbirth and postnatal mortality, and decreased growth and physical development, were observed in the offspring of females treated with doses of 7 mg/kg/day or greater during the latter part of gestation and throughout lactation. There was no evidence of maternal toxicity at this dose. The no-effect dose for offspring development was 1 mg/kg/day. When the adverse effects on offspring viability and growth were examined in a cross-fostering study, they appeared to result from both in utero and lactational exposure to the drug.
There are no studies of zaleplon in pregnant women; therefore, Sonata is not recommended for use in women during pregnancy.
LABOR AND DELIVERY: Sonata has no established use in labor and delivery.
NURSING MOTHERS: A study in lactating mothers indicated that the clearance and half-life of zaleplon is similar to that in young normal subjects. A small amount of zaleplon is excreted in breast milk, with the highest excreted amount occurring during a feeding at approximately 1 hour after Sonata administration. Since the small amount of the drug from breast milk may result in potentially important concentrations in infants, and because the effects of zaleplon on a nursing infant are not known, *it is recommended that nursing mothers not take Sonata.*
PEDIATRIC USE: The safety and effectiveness of Sonata in pediatric patients have not been established.
GERIATRIC USE: A total of 628 patients in double-blind, placebo-controlled, parallel-group clinical trials who received Sonata were at least 65 years of age; of these, 311 received 5 mg and 317 received 10 mg. In both sleep laboratory and outpatient studies, elderly patients with insomnia responded to a 5-mg dose with a reduced sleep latency, and thus 5 mg is the recommended dose in this population. During short-term treatment (14 night studies) of elderly patients with Sonata, no *adverse event with a frequency of at least 1% occurred at a significantly higher rate* with either 5 mg or 10 mg Sonata than with placebo.
Adverse Reactions: ADVERSE FINDINGS OBSERVED IN SHORT-TERM, PLACEBO-CONTROLLED TRIALS—*Adverse Events Associated with Discontinuation of Treatment:* In premarketing placebo-controlled, parallel-group phase 2-3 clinical trials, 3.1% of 744 patients who received placebo and 3.5% of 2,069 patients who received Sonata discontinued treatment because of an adverse clinical event. This difference was not statistically significant. No event that resulted in discontinuation occurred at a rate of ≥ 1%.
Adverse Events Occurring at an Incidence of 1% or More Among Sonata 20 Mg-treated Patients: Table 1 enumerates, for a pool of three placebo-controlled 28-night studies of Sonata at doses of 5 or 10 mg and 20 mg, the incidence of treatment emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with Sonata 20 mg where the incidence in patients treated with Sonata 20 mg was greater than the incidence in placebo-treated patients.

TABLE 1: Incidence (%) of Treatment-emergent Adverse Events in Long-term (28 Nights) Placebo-controlled Clinical Trials of Sonata[1]

Body system Preferred term	Placebo (n = 277)	Sonata 5 or 10 mg (n = 513)	Sonata 20 mg (n = 273)
Body as a whole			
Abdominal pain	4	5	6
Asthenia	5	5	8
Fever	1	2	2
Headache	31	28	38
Malaise	<1	<1	2
Photosensitivity reaction	<1	<1	1
Digestive system			
Anorexia	<1	<1	2
Colitis	0	0	1
Dyspepsia	5	4	7
Nausea	7	7	8
Metabolic and nutritional			
Peripheral edema	<1	<1	1
Musculoskeletal system			
Myalgia	4	7	5
Nervous system			
Amnesia	1	2	4
Anxiety	2	<1	3
Depersonalization	<1	<1	2
Dizziness	7	7	8
Hallucinations	<1	<1	1
Hypesthesia	0	<1	2
Paresthesia	1	3	3
Somnolence	3	5	5
Tremor	1	2	2
Vertigo	<1	<1	1
Respiratory system			
Epistaxis	0	<1	1
Special senses			
Abnormal vision	<1	<1	2
Ear pain	0	<1	1
Eye pain	3	4	4
Hyperacusis	<1	2	2
Parosmia	1	<1	2
Urogenital system			
Dysmenorrhea	2	2	4

1: Events for which the incidence for Sonata 20 mg-treated patients was at least 1% and greater than the incidence among placebo-treated patients. Incidence greater than 1% has been rounded to the nearest whole number.

OTHER ADVERSE EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF SONATA: Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **Adverse Reactions** section reported by patients treated with Sonata at doses in a range of 5 to 20 mg/day during premarketing phase 2 and 3 clinical trials throughout the United States, Canada, and Europe including approximately 2800 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, and *those events for which a drug cause was remote, and those event terms which* were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with Sonata, they were not necessarily caused by it.
Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in less than 1/100 patients but at least 1/1,000 patients; **rare** events are those occurring in fewer than 1/1,000 patients.
Body as a whole - **Frequent:** back pain, chest pain; **Infrequent:** chest pain substernal, chills, face edema, generalized edema, hangover effect, neck rigidity.
Cardiovascular system - **Frequent:** migraine, **Infrequent:** angina pectoris, bundle branch block, hypertension, hypotension, palpitation, syncope, tachycardia, vasodilatation, ventricular extrasystoles; **Rare:** bigeminy, cerebral ischemia, cyanosis, pericardial effusion, postural hypotension, pulmonary embolus, sinus bradycardia, thrombophlebitis, ventricular tachycardia. Digestive system - **Frequent:** constipation, dry mouth; **Infrequent:** eructation, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, glossitis, increased appetite, melena, mouth ulceration, rectal hemorrhage, stomatitis; **Rare:** aphthous stomatitis, biliary pain, bruxism, cardiospasm, cheilitis, cholelithiasis, duodenal ulcer, dysphagia, enteritis, gum hemorrhage, increased salivation, intestinal obstruction, liver function tests abnormal, peptic ulcer, tongue discoloration, tongue edema, ulcerative stomatitis. Endocrine system - **Rare:** diabetes mellitus, goiter, hypothyroidism. Hemic and lymphatic system - **Infrequent:** anemia, ecchymosis, lymphadenopathy; **Rare:** eosinophilia, leukocytosis, lymphocytosis, purpura. Metabolic and nutritional - **Infrequent:** edema, gout, hypercholesteremia, thirst, weight gain; **Rare:** bilirubinemia, hyperglycemia, hyperuricemia, hypoglycemia, hypoglycemic reaction, ketosis, SGOT increased, SGPT increased, weight loss. Musculoskeletal system - **Frequent:** arthritis; **Infrequent:** arthrosis, bursitis, joint disorder (mainly swelling, stiffness, and pain), myasthenia, tenosynovitis; **Rare:** myositis, osteoporosis. Nervous system - **Frequent:** depression, hypertonia, nervousness, thinking abnormal (mainly difficulty concentrating); **Infrequent:** abnormal gait, agitation, apathy, ataxia, circumoral paresthesia, confusion, emotional lability, euphoria, hyperesthesia, hyperkinesia, hypotonia, incoordination, insomnia, libido decreased, neuralgia, nystagmus; ***Rare:*** *CNS stimulation, delusions, dysarthria, dystonia, facial paralysis, hostility,* hypokinesia, myoclonus, neuropathy, psychomotor retardation, ptosis, reflexes decreased, reflexes increased, sleep talking, sleep walking, slurred speech, stupor, trismus. Respiratory system - **Frequent:** bronchitis; **Infrequent:** asthma, dyspnea, laryngitis, pneumonia, snoring, voice alteration; **Rare:** apnea, hiccup, hyperventilation, pleural effusion, sputum increased. Skin and appendages - **Frequent:** pruritus, rash; **Infrequent:** acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, skin hypertrophy, sweating, urticaria, vesiculobullous rash; **Rare:** melanosis, psoriasis, pustular rash, skin discoloration. Special senses - **Frequent:** conjunctivitis; **Infrequent:** diplopia, dry eyes, photophobia, tinnitus, watery eyes; **Rare:** abnormality of accommodation, blepharitis, cataract specified, corneal erosion, deafness, eye hemorrhage, glaucoma, labyrinthitis, retinal detachment, taste loss, visual field defect. Urogenital system - **Infrequent:** bladder pain, breast pain, cystitis, decreased urine stream, dysuria, hematuria, impotence, kidney calculus, kidney pain, menorrhagia, metrorrhagia, urinary frequency, urinary incontinence, urinary urgency, vaginitis; **Rare:** albuminuria, delayed menstrual period, leukorrhea, menopause, urethritis, urinary retention, vaginal hemorrhage.
Drug Abuse and Dependence—*CONTROLLED SUBSTANCE CLASS:* Sonata is classified as a Schedule IV controlled substance by federal regulation.
ABUSE, DEPENDENCE, AND TOLERANCE: *Abuse*—Two studies assessed the abuse liability of Sonata at doses of 25, 50, and 75 mg in subjects with known histories of sedative drug abuse. The results of these studies indicate that Sonata has an abuse potential similar to benzodiazepine and benzodiazepine-like hypnotics.
Dependence: The potential for developing physical dependence on Sonata and a subsequent withdrawal syndrome was assessed in controlled studies of 14- and 28-day durations and in open-label studies of 6- and 12-month durations by examining for the emergence of rebound insomnia following drug discontinuation. Some patients (mostly those treated with 20 mg) experienced a mild rebound insomnia on the first night following withdrawal that appeared to be resolved by the second night. The use of the Benzodiazepine Withdrawal Symptom Questionnaire and examination for any other withdrawal emergent events did not detect any other evidence for a withdrawal syndrome following abrupt discontinuation of Sonata therapy in pre-marketing studies. However, available data cannot provide a reliable estimate of the incidence of dependence during treatment at recommended doses of Sonata. Other sedative/hypnotics have been associated with various signs and symptoms following abrupt discontinuation, ranging from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. Seizures have been observed in two patients, one of whom had a prior seizure, in clinical trials with Sonata. Seizures and death have been seen following the withdrawal of zaleplon from animals at doses many times higher than those proposed for human use. Because individuals with a history of addiction to, or abuse of, drugs or alcohol are *at risk of habituation and dependence, they should be under careful surveillance* when receiving Sonata or any other hypnotic. *Tolerance:* Possible tolerance to the hypnotic effects of Sonata 10 and 20 mg was assessed by evaluating time to sleep onset with Sonata compared with placebo in two placebo-controlled 28-day studies. No development of tolerance to Sonata was observed for time to sleep onset over 4 weeks.
OVERDOSAGE: There is limited pre-marketing clinical experience with the effects of an overdosage of Sonata. Two cases of overdose were reported. One was the accidental ingestion by a 2½ year old boy of 20-40 mg of zaleplon. The second was a 20 year old man who took 100 mg zaleplon plus 2.25 mg of triazolam. Both were treated and recovered uneventfully.
Signs and Symptoms: Signs and symptoms of overdose effects of CNS depressants can be expected to present as exaggerations of the pharmacological effects noted in preclinical testing. Overdose is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion, and lethargy; in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma, and very rarely death.
Recommended Treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Animal studies suggest that flumazenil is an antagonist to zaleplon. However, there is no premarketing clinical experience with the use of flumazenil as an antidote to a Sonata overdose. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention.
Poison Control Center: As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdosage.
Based on Sonata CI 6001-1 issued August 13, 1999

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Patients should remain inactive for 4 or more hours after taking SONATA.
Among the most common side effects are headache, dizziness, and somnolence.[2]
Until patients know how they will react to sleep agents, they should not engage in activities requiring mental alertness or motor coordination (e.g., driving or operating machinery) after taking SONATA or any sleep agent.
Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if hypnotics are taken for more than 2 to 3 weeks.
Prescriptions for SONATA should not exceed a 1-month supply.

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References: 1. Elie R, Rüther E, Farr I, et al. Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. *J Clin Psychiatry*. 1999;60:536–544.
2. SONATA® (zaleplon) Prescribing Information, Wyeth-Ayerst Laboratories, Philadelphia, Pa.

Please visit our Web site at www.sonatasleep.com

Please see brief summary of Prescribing Information on adjacent page.

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Feature Articles

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December 2000

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Custom-tailored dosing

In two 6- to 8-week placebo-controlled clinical 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.

EPS with RISPERDAL, while dose-dependent, are comparable to placebo at doses ≤6 mg/day and differ significantly from placebo at doses >6 mg/day. Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia; if its signs and symptoms appear, discontinuation of RISPERDAL should be considered.

Orthostatic hypotension was reported infrequently (<1%) in clinical trials; its risk may be minimized by following the recommended RISPERDAL dose titration regimen.

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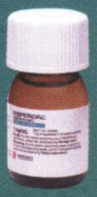

to special populations*

*Patients who are elderly or who are renally or hepatically impaired.

Reference:
1. IMS America, 12/99.

Please see brief summary of Prescribing Information on adjacent page.

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tablets and oral solution 1 mg/mL RISPERIDONE

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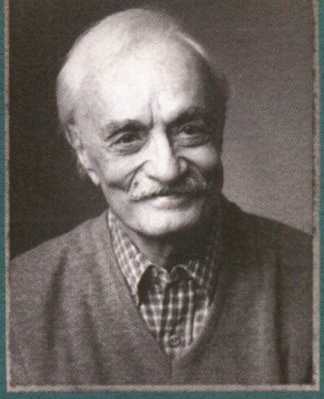

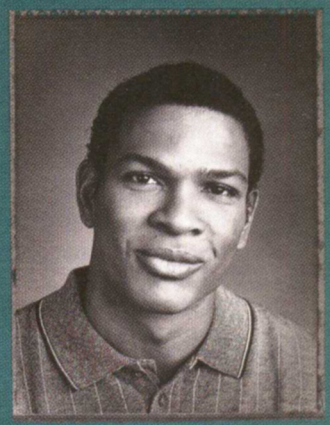

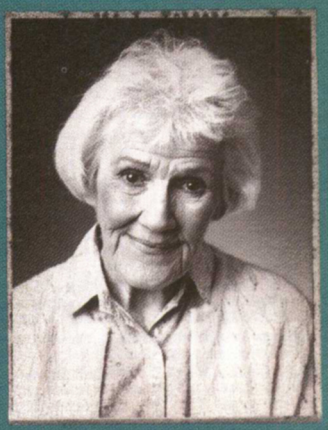

Risperdal®

tablets and oral solution 1 mg/mL 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, gastroesophageal 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.

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