DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 27 2000

TRANSMITTED VIA FACSIMILE

Nanette E. Holston
Manager, U.S. Regulatory Affairs
Wyeth-Ayerst Research
P.O. Box 8299
Philadelphia, PA 19101-8299

RE: NDA #20-859
Sonata (zaleplon) Capsules
MACMIS #8573

Dear Ms. Holston:

Through routine monitoring and surveillance, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has become aware of a journal advertisement and a Brief Summary (ID# 78562-00) for Sonata that are false or misleading, and in violation of the Federal Food, Drug, and Cosmetic Act. Specifically, the advertisement and the Brief Summary are misleading because they omit the caveat from the Indications and Usage section of the approved product labeling (PI) that Sonata "has not been shown to increase total sleep time or decrease the number of awakenings."

To address this objection, DDMAC recommends that Wyeth-Ayerst Laboratories (Wyeth) do the following:

1. Immediately discontinue the use of this journal advertisement, Brief Summary, and any other promotional material with the same or similar issues. This would include evaluating other promotional material for failure to convey this caveat of Sonata's indication.

2. Respond to this letter, in writing, by February 7, 2000. Wyeth's response should include a statement of its intent to comply with the above, a list of all promotional materials with the same or similar issues, and Wyeth's methods for discontinuing these promotional materials.

If you have any questions or comments, please contact Dr. Lisa L. Stockbridge by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, rm. 17B-20, 5600 Fishers Lane,

Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 8573 in addition to the NDA number.

Sincerely, /S/

Lisa L. Stockbridge, Ph.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

ANNOUNCING

The First Solution for the Short-Term Treatment of Insomnia With Flexible Administration

Good Night's Sleep

the Ability to Function[1]

Patients need to remain in bed 4 or more hours before becoming active again.

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.

During treatment lasting 28 nights, with SONATA 5 or 10 mg, among the most common side effects were headache (28% vs 31% for placebo), dizziness (7% vs 7% for placebo), and somnolence (5% vs 3% for placebo).[2] Hypnotics should generally be limited to 7 to 10 days of use, and re-evaluation 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.

References: 1. Data on file, Wyeth-Ayerst Laboratories, Philadelphia, Pa.
2. SONATA (zaleplon) Prescribing Information, Wyeth-Ayerst Laboratories, Philadelphia, Pa.

Please see brief summary of Prescribing Information on adjacent page.

E

sonata®

ZALEPLON CIV

CAPSULES

Wake Up Ready to Function

Brief Summary
Sonata® (zaleplon) Capsules
See package insert for full prescribing information.
Indications and Usage: Sonata is indicated for the short-term treatment of insomnia. Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation of the patient is recommended if they are to be taken for more than 2 to 3 weeks. Sonata should not be prescribed in quantities exceeding a 1-month supply (see **Warnings**).
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 (see **Dosage and Administration**). 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 (see **Dosage and Administration**). 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 (see **Dosage and Administration**). 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 (see **Dosage and Administration**).
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+I- 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. This dose is equivalent to 49 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. 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. These doses are equivalent to 49 (rat) and 48 (rabbit) times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. 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	3
Headache	31	28	28
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	8
Nervous system			
Amnesia	1	2	4
Anxiety	2	<1	3
Depersonalization	<1	<1	2
Dizziness	7	7	6
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 premarketing 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 drug or alcohol abuse or dependence 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 21½ year old boy of 20-40 mg of zaleplon. The second was a 22 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

WYETH-AYERST LABORATORIES
Philadelphia, PA 19101