

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine



**Prodromal Schizophrenia:
The Dilemma of Prediction and Early Intervention**

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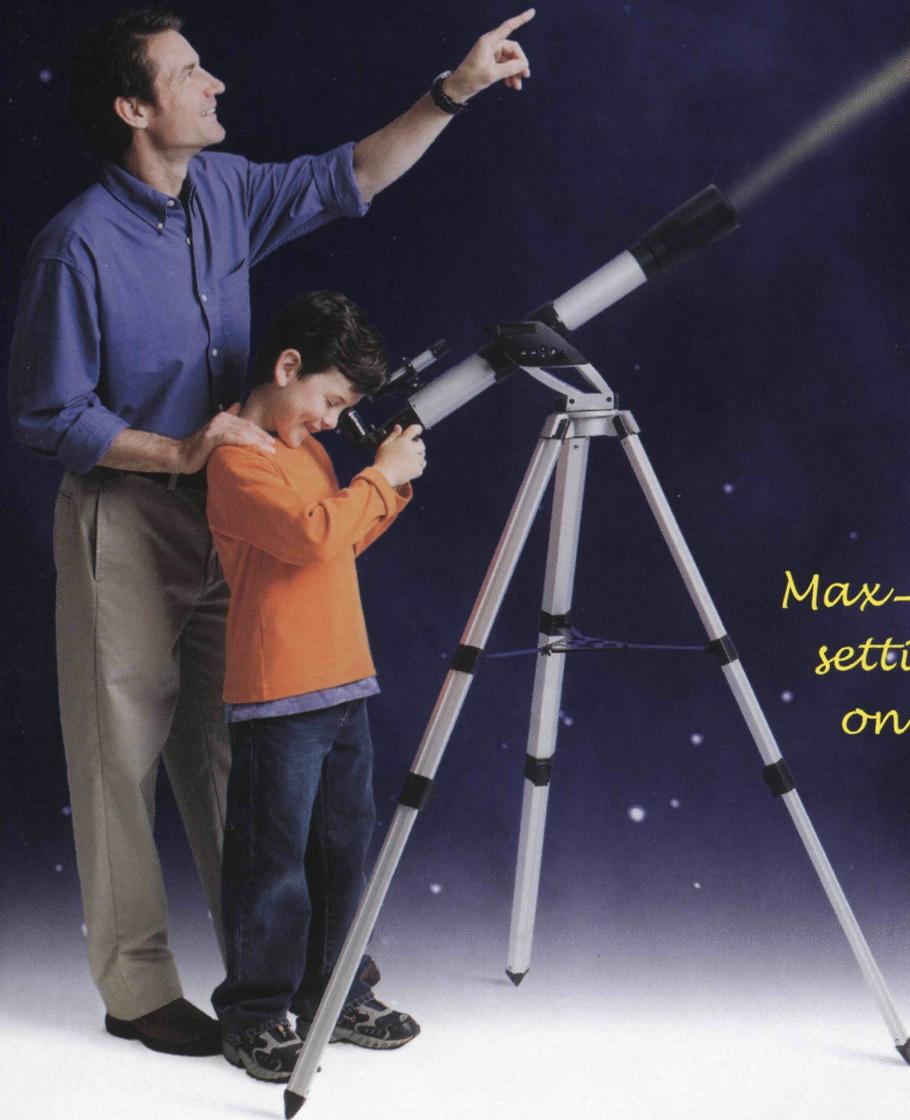
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**Severity of Obsessive-Compulsive Symptoms
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C. Cruz-Fuentes, C. Blas, L. Gonzalez, B. Camarena, and H. Nicolini

In the treatment of ADHD...

AIM



*Max—
setting his sights
on astronomy*

The most common adverse events included loss of appetite, insomnia, abdominal pain, and emotional lability.

As with other psychostimulants indicated for ADHD, there is a potential for exacerbating motor and phonic tics and Tourette's syndrome. A side effect seen with the amphetamine class is psychosis. Caution also should be exercised in patients with a history of psychosis.

HIGHER

With efficacy that goes beyond adequate symptom control—to help them reach new heights

- Reduces symptoms to a level comparable to that of non-ADHD children¹
- Effectively addresses the core impairments of ADHD—inattention, hyperactivity, and impulsivity²
- Once-daily dosing provides day-long improvement in academic productivity and social functioning^{3,4}

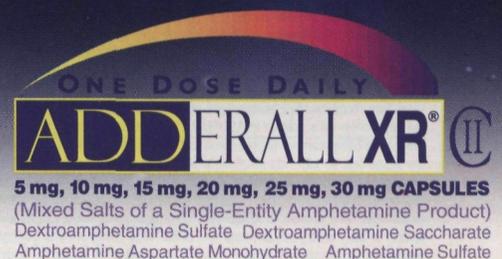
Please see references and brief summary of prescribing information on adjacent page.

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Reach new heights

Abuse of amphetamines may lead to dependence. ADDERALL XR is contraindicated in patients with symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism and glaucoma, known hypersensitivity to this class of compounds, agitated states, history of drug abuse, or current or recent use of MAO inhibitors. ADDERALL XR should be prescribed with close physician supervision.

References: I. Ambrosini PJ, Lopez FA, Chandler MC, et al. Safety and efficacy of ADDERALL XR in pediatric ADHD: results of an open-label community assessment trial. Poster presented at: 14th Annual CHADD International Conference; October 17, 2002; Miami Beach, Fla. 2. Spencer T, Biederman J, Wilens T, et al. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *J Am Acad Child Adolesc Psychiatry*; 1996;35:409-432. 3. Lopez FA, Ambrosini PJ, Chandler MC, et al. ADDERALL XR in pediatric ADHD: quality of life measures from an open-label community assessment trial. Poster presented at: 14th Annual CHADD International Conference; October 17, 2002; Miami Beach, Fla. 4. Lopez FA, Chandler MC, Biederman J, et al. Long-term Adderall XR treatment improves quality of life in ADHD children. Poster presented at: 156th Annual Meeting of the American Psychiatric Association; May 21, 2003; San Francisco, Calif.

BRIEF SUMMARY: Consult the full prescribing information for complete product information.

ADDERALL XR® CAPSULES

Cl Rx Only

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

INDICATIONS ADDERALL XR® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of ADDERALL XR® in the treatment of ADHD was established on the basis of two controlled trials of children aged 6 to 12 who met DSM-IV criteria for ADHD, along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance. **CONTRAINDICATIONS** Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result). **WARNINGS Psychosis:** Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. **Long-Term Suppression of Growth:** Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

PRECAUTIONS General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose. **Hypertension and other Cardiovascular Conditions:** Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR®, especially patients with hypertension. **Tics:** Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications. **Information for Patients:** Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly. **Drug Interactions: Acidifying agents—**Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) lower absorption of amphetamines. **Urinary acidifying agents—**These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines. **Adrenergic blockers—**Adrenergic blockers are inhibited by amphetamines. **Alkalinizing agents—**Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. **Co-administration of ADDERALL XR® and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines. Antidepressants, tricyclic—**Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or proprietyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated. **MAO inhibitors—**MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results. **Antihistamines—**Amphetamines may counteract the sedative effect of antihistamines. **Antihypertensives—**Amphetamines may antagonize the hypotensive effects of antihypertensives. **Chlorpromazine—**Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning. **Ethosuximide—**Amphetamines may delay intestinal absorption of ethosuximide. **Haloperidol—**Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines. **Lithium carbonate—**The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate. **Meperidine—**Amphetamines potentiate the analgesic effect of meperidine. **Methamphetamine therapy—**Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methamphetamine therapy. **Norepinephrine—**Amphetamines enhance the adrenergic effect of norepinephrine. **Phenobarbital—**Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action. **Phenytoin—**Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action. **Propoxyphene—**In cases of propoxyphene overdose, amphetamine CNS stimulation is potentiated and fatal convulsions can occur. **Veratrum alkaloids—**Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations. **Carcinogenesis/Mutagenesis and Impairment of Fertility:** No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day on a mg/m² body surface area basis. Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays. Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m² body surface area basis). **Pregnancy:** Pregnancy Category C. Amphetamine, in the enantiomer ratio present in ADDERALL® (d- to l- ratio of 3:1), had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day on a mg/m² body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times the maximum recommended human dose of 30 mg/day on a mg/m² basis) or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity. A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-), at doses similar to those used clinically, can result in long-term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function. There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (water association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects:** Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by

dysphoria, including agitation, and significant lassitude. **Usage in Nursing Mothers:** Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing. **Pediatric Use:** ADDERALL XR® is indicated for use in children 6 years of age and older. **Use in Children Under Six Years of Age:** Effects of ADDERALL XR® in 3-5 year olds have not been studied. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age. **Geriatric Use:** ADDERALL XR® has not been studied in the geriatric population. **ADVERSE EVENTS** The premarketing development program for ADDERALL XR® included exposures in a total of 685 participants in clinical trials (615 patients, 70 healthy adult subjects). These participants received ADDERALL XR® at daily doses up to 30 mg. The 615 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and one single-dose clinical pharmacology study (N=20). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

Adverse events associated with discontinuation of treatment: In two placebo-controlled studies of up to 5 weeks duration, 2.4% (10/425) of ADDERALL XR® treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of ADDERALL XR® in controlled and uncontrolled, multiple-dose clinical trials (N=595) are presented below. Over half of these patients were exposed to ADDERALL XR® for 12 months or more.

Adverse event	% of patients discontinuing (N=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight loss	1.2
Emotional lability	1.0
Depression	0.7

Adverse events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients treated with ADDERALL XR® or placebo are presented in the table below. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1 Adverse Events Reported by More Than 1% of Patients Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 584 Patient Clinical Study

Body System	Preferred Term	ADDERALL XR® (N=374)	Placebo (N=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Lability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
	Weight Loss	4%	0%

The following adverse reactions have been associated with amphetamine use: Cardiovascular: Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome. Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects. Allergic: Urticaria. Endocrine: Impotence, changes in libido. **DRUG ABUSE AND DEPENDENCE** ADDERALL XR® is a Schedule II controlled substance. Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. **OVERDOSSAGE** Individual patient response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses. Symptoms: Manifestations of acute overdose with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma. Treatment: Consult with a Certified Poison Control Center for up-to-date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdose, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication. The prolonged release of mixed amphetamine salts from ADDERALL XR® should be considered when treating patients with overdose. Dispense in a tight, light-resistant container as defined in the USP. Store at 25° C (77° F). Excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature]. Manufactured by DSM Pharmaceuticals Inc., Greenville, North Carolina 27834. Distributed and marketed by Shire US Inc., Newport, KY 41071. For more information call 1-800-828-2088 or visit www.adderallxr.com. ADDERALL® is registered in the US Patent and Trademark Office.

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Introduction

CNS Spectrums is an *Index Medicus* journal that publishes original scientific literature and reviews on a wide variety of neuroscientific topics of interest to the clinician on a monthly basis. Our mission is to provide physicians with an editorial package that will enhance and increase their understanding of neuropsychiatry; therefore, manuscripts that address crossover issues between neurology and psychiatry will be given immediate priority.

Scope of Manuscripts

CNS Spectrums will consider and encourages the following types of articles for publication:

Original Research presents methodologically sound original data.

Reviews are comprehensive articles summarizing and synthesizing the literature on various neuropsychiatric topics and presented in a scholarly and clinically relevant fashion. Diagnostic and treatment algorithms should be designed to aid the clinician in diagnosis and treatment.

Case Reports, single or multiple, are encouraged for publication.

Letters to the Editor will be considered and are encouraged for publication. All letters will be edited for style, clarity, and length.

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General Information Two copies of the manuscript with a letter on the author's letterhead should be submitted to Jack M. Gorman, MD, Editor (or, in Europe, to Joseph Zohar, MD, International Editor), c/o MBL Communications, 333 Hudson Street, 7th Floor, New York, NY 10013. Authors are also required to submit their manuscripts on computer disk in Microsoft Word format. Disks should be labeled with the word processing program, title of paper, and lead author's name. Accepted manuscripts will be edited for clarity and style.

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Length Reviews and Original Research should not exceed 5,000 words (excluding References). Diagnostic and treatment algorithms should contain an introduction, flowcharts or a series of graphs, and a concise summary. Letters should not exceed 1,500 words. Single

Case Reports should not exceed 3,750 words and may be submitted with a photograph, if applicable.

Please note: If your article is Original Research, it should be formatted as: Abstract (100–200 words); Introduction, Methods; Findings; Discussion; Conclusion; References (numbered and comprehensive list).

Spacing and Pagination One space should be left after commas and periods. Manuscripts should be double-spaced and numbered.

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Figures/Tables Please provide original figures and/or tables if content is amenable to it.

References Please use American Medical Association style. References should be superscripted in text, then numbered, and comprehensive in list. See the following examples:

1. Jones J. Necrotizing Candida esophagitis. *JAMA*. 1980;244:2190-2191.
2. Stryer L. *Biochemistry*. 2nd ed. San Francisco, Calif: WH Freeman Co; 1980:559-596.
3. Alzheimer's Disease Cooperative Study. Valproate protocol. Available at: http://adcs.ucsd.edu/VP_Protocol.htm. Accessed October 15, 2003.

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- A brief abstract of the article
- Six CME multiple-choice questions with answers
- Three to six focus points
- Disk labeled with the word processing program, title of paper, and lead author's name
- Names and affiliations of three to five potential peer reviewers

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MANIA IN BIPOLAR DISORDER**

**Well
Accepted!**

Another great reason to prescribe

- **Effective** so patients improve¹⁻³
- **Trusted tolerability** so patients can stay on treatment^{1,4,5}

The safety and efficacy of SEROQUEL in pediatric patients have not been established.

Patients should be periodically reassessed to determine the need for continued treatment.

Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension. A rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported with this class of medications, including SEROQUEL.

There have been reports of diabetes mellitus and hyperglycemia-related adverse events associated with the use of atypical antipsychotics, including SEROQUEL.

The most common adverse events associated with the use of SEROQUEL were somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, SGPT increase, dyspepsia, and weight gain.

In bipolar mania trials, withdrawal rates due to adverse events were similar to placebo for SEROQUEL as monotherapy (SEROQUEL 5.7%, placebo 5.1%) and adjunct therapy (SEROQUEL plus lithium or divalproex 3.6%, lithium or divalproex alone 5.9%).

References: 1. SEROQUEL® (quetiapine fumarate) Prescribing Information, Rev 01/04, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware.

2. Data on file, DA-SER-13, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware. 3. Data on file, DA-SER-15, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware. 4. Data on file, DA-SER-14, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware. 5. Data on file, DA-SER-16, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware.

 **Seroquel**[®]
quetiapine fumarate
25 mg, 100 mg, 200 mg & 300 mg tablets

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AstraZeneca Pharmaceuticals LP

To prevent medication errors, write "**SEROQUEL**" clearly on your Rx pad. Spell "**SEROQUEL**" clearly over the phone.

Please see Brief Summary of Prescribing Information on following page.

First-line treatment

www.SEROQUEL.com

217350 1/04

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<https://doi.org/10.1017/S1092852900002698> Published online by Cambridge University Press

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EDITORIAL MISSION

CNS Spectrums' editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients, and original research and reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. The journal's goal is to serve as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of central nervous system disease, illness, or trauma.

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

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Founded in 1996, *CNS Spectrums* is an *Index Medicus* journal and is available on MEDLINE under the citation *CNS Spectr.* It is available online at www.cnsspectrums.com.

CNS Spectrums (ISSN 1092-8529) is published monthly by MBL Communications, Inc. 333 Hudson Street, 7th Floor, New York, NY 10013.

One-year subscription rates: domestic \$120; foreign \$185; in-training \$75. For subscriptions: Phone: 212-328-0800; Fax: 212-328-0600; Web: www.cnsspectrums.com.

Postmaster: Send address changes to *CNS Spectrums* c/o PPS Medical Marketing Group 264 Passaic Avenue, Fairfield, NJ 07004-2595.

For editorial inquiries, please fax us at 212-328-0600 or e-mail us at jrr@mblcommunications.com. For bulk reprint purchases, please contact: Kelly J. Staley at kjs@mblcommunications.com.

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Please see brief summary of Prescribing Information on adjacent page.

References: 1. ZONEGRAN[®] Prescribing Information, Elan Pharmaceuticals, 2002. 2. Brodie M, Wilson E, Smith D, et al. Steady-state drug interaction study of zonisamide and lamotrigine in epileptic patients. *Neurology*. 2001;56(3):A337 (abstract). 3. Data on file. Elan Pharmaceuticals, Inc.

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CONTRAINDICATIONS

ZONEGRAN is contraindicated in patients who have demonstrated hypersensitivity to sulfonamides or zonisamide.

WARNINGS

Potentially Fatal Reactions to Sulfonamides: Fatalities have occurred, although rarely, as a result of severe reactions to sulfonamides [zonisamide is a sulfonamide] including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Such reactions may occur when a sulfonamide is readministered irrespective of the route of administration. If signs of hypersensitivity or other serious reactions occur, discontinue zonisamide immediately. Specific experience with sulfonamide-type adverse reaction to zonisamide is described below.

Serious Skin Reactions: Consideration should be given to discontinuing ZONEGRAN in patients who develop an otherwise unexplained rash. If the drug is not discontinued, patients should be observed frequently. Seven deaths from severe rash [i.e. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)] were reported in the first 11 years of marketing in Japan. All of the patients were receiving other drugs in addition to zonisamide. In post-marketing experience from Japan, a total of 49 cases of SJS or TEN have been reported, a reporting rate of 46 per million patient-years of exposure. Although this rate is greater than background, it is probably an underestimate of the true incidence because of under-reporting. There were no confirmed cases of SJS or TEN in the US, European, or Japanese development programs.

In the US and European randomized controlled trials, 6 of 269 (2.2%) zonisamide patients discontinued treatment because of rash compared to none on placebo. Across all trials during the US and European development, rash that led to discontinuation of zonisamide was reported in 1.4% of patients (12.0 events per 1000 patient-years of exposure). During Japanese development, serious rash or rash that led to study drug discontinuation was reported in 2.0% of patients (27.8 events per 1000 patient years). Rash usually occurred early in treatment, with 85% reported within 16 weeks in the US and European studies and 90% reported within two weeks in the Japanese studies. There was no apparent relationship of dose to the occurrence of rash.

Serious Hematologic Events: Two confirmed cases of aplastic anemia and one confirmed case of agranulocytosis were reported in the first 11 years of marketing in Japan, rates greater than generally accepted background rates. There were no cases of aplastic anemia and two confirmed cases of agranulocytosis in the US, European, or Japanese development programs. There is inadequate information to assess the relationship, if any, between dose and duration of treatment and these events.

Oligohidrosis and Hyperthermia in Pediatric Patients:

Oligohidrosis, sometimes resulting in heat stroke and hospitalization, is seen in association with zonisamide in pediatric patients.

During the pre-approval development program in Japan, one case of oligohidrosis was reported in 403 pediatric patients, an incidence of 1 case per 285 patient-years of exposure. While there were no cases reported in the US or European development programs, fewer than 100 pediatric patients participated in these trials.

In the first 11 years of marketing in Japan, 38 cases were reported, an estimated reporting rate of about 1 case per 10,000 patient-years of exposure. In the first year of marketing in the US, 2 cases were reported, an estimated reporting rate of about 12 cases per 10,000 patient-years of exposure. These rates are underestimates of the true incidence because of under-reporting. There has also been one report of heat stroke in an 18-year-old patient in the US.

Decreased sweating and an elevation in body temperature above normal characterized these cases. Many cases were reported after exposure to elevated environmental temperatures. Heat stroke, requiring hospitalization, was diagnosed in some cases. There have been no reported deaths.

Pediatric patients appear to be at an increased risk for zonisamide-associated oligohidrosis and hyperthermia. Patients, especially pediatric patients, treated with ZONEGRAN should be monitored closely for evidence of decreased sweating and increased body temperature, especially in warm or hot weather. Caution should be used when zonisamide is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, carbonic anhydrase inhibitors and drugs with anticholinergic activity.

The practitioner should be aware that the safety and effectiveness of zonisamide in pediatric patients have not been established, and that zonisamide is not approved for use in pediatric patients.

Seizures on Withdrawal: As with other AEDs, abrupt withdrawal of ZONEGRAN in patients with epilepsy may precipitate increased seizure frequency or status epilepticus. Dose reduction or discontinuation of zonisamide should be done gradually.

Teratogenicity: Women of child bearing potential who are given zonisamide should be advised to use effective contraception. Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. A variety of fetal abnormalities, including cardiovascular defects, and embryo-fetal deaths occurred at maternal plasma levels similar to or lower than therapeutic levels in humans. These findings suggest that the use of ZONEGRAN during pregnancy in humans may present a significant risk to the fetus (see PRECAUTIONS, Pregnancy subsection). It cannot be said with any confidence, however, that even mild seizures do not pose some hazards to the developing fetus. Zonisamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Cognitive/ Neuropsychiatric Adverse Events: Use of ZONEGRAN was frequently associated with central nervous system-related adverse events. The most significant of these can be

classified into three general categories: 1) psychiatric symptoms, including depression and psychosis, 2) psychomotor slowing, difficulty with concentration, and speech or language problems, in particular, word-finding difficulties, and 3) somnolence or fatigue.

In placebo-controlled trials, 2.2% of patients discontinued ZONEGRAN or were hospitalized for depression compared to 0.4% of placebo patients, while 1.1% of ZONEGRAN and 0.4% of placebo patients attempted suicide. Among all epilepsy patients treated with ZONEGRAN, 1.4% were discontinued and 1.0% were hospitalized because of reported depression or suicide attempts. In placebo-controlled trials, 2.2% of patients discontinued ZONEGRAN or were hospitalized due to psychosis or psychosis-related symptoms compared to none of the placebo patients. Among all epilepsy patients treated with ZONEGRAN, 0.9% were discontinued and 1.4% were hospitalized because of reported psychosis or related symptoms.

Psychomotor slowing and difficulty with concentration occurred in the first month of treatment and were associated with doses above 300 mg/day. Speech and language problems tended to occur after 6–10 weeks of treatment and at doses above 300 mg/day. Although in most cases these events were of mild to moderate severity, they at times led to withdrawal from treatment.

Somnolence and fatigue were frequently reported CNS adverse events during clinical trials with ZONEGRAN. Although in most cases these events were of mild to moderate severity, they led to withdrawal from treatment in 0.2% of the patients enrolled in controlled trials. Somnolence and fatigue tended to occur within the first month of treatment. Somnolence and fatigue occurred most frequently at doses of 300–500 mg/day. Patients should be cautioned about this possibility and special care should be taken by patients if they drive, operate machinery, or perform any hazardous task.

PRECAUTIONS

General: Somnolence is commonly reported, especially at higher doses of ZONEGRAN (see WARNINGS: Cognitive/ Neuropsychiatric Adverse Events subsection). Zonisamide is metabolized by the liver and eliminated by the kidneys; caution should therefore be exercised when administering ZONEGRAN to patients with hepatic and renal dysfunction (see CLINICAL PHARMACOLOGY, Special Populations subsection of full Prescribing Information).

Kidney Stones: Among 991 patients treated during the development of ZONEGRAN, 40 patients (4.0%) with epilepsy receiving ZONEGRAN developed clinically possible or confirmed kidney stones [e.g. clinical symptomatology, sonography, etc.], a rate of 34 per 1000 patient-years of exposure (40 patients with 1168 years of exposure). Of these, 12 were symptomatic, and 28 were described as possible kidney stones based on sonographic detection. In nine patients, the diagnosis was confirmed by a passage of a stone or by a definitive sonographic finding. The rate of occurrence of kidney stones was 28.7 per 1000 patient-years of exposure in the first six months, 62.6 per 1000 patient-years of exposure between 6 and 12 months, and 24.3 per 1000 patient-years of exposure after 12 months of use. There are no normative sonographic data available for either the general population or patients with epilepsy. The clinical significance of the sonographic finding is unknown. The analyzed stones were composed of calcium or urate salts. In general, increasing fluid intake and urine output can help reduce the risk of stone formation, particularly in those with predisposing risk factors. It is unknown, however, whether these measures will reduce the risk of stone formation in patients treated with ZONEGRAN.

Effect on Renal Function: In several clinical studies, zonisamide was associated with a statistically significant 8% mean increase from baseline of serum creatinine and blood urea nitrogen (BUN) compared to essentially no change in the placebo patients. The increase appeared to persist over time but was not progressive; this has been interpreted as an effect on glomerular filtration rate (GFR). There were no episodes of unexplained acute renal failure in clinical development in the US, Europe, or Japan. The decrease in GFR appeared within the first 4 weeks of treatment. In a 30-day study, the GFR returned to baseline within 2–3 weeks of drug discontinuation. There is no information about reversibility, after drug discontinuation, of the effects on GFR after long-term use. ZONEGRAN should be discontinued in patients who develop acute renal failure or a clinically significant sustained increase in the creatinine/BUN concentration. ZONEGRAN should not be used in patients with renal failure (estimated GFR < 50 mL/min) as there has been insufficient experience concerning drug dosing and toxicity.

Sudden Unexplained Death in Epilepsy: During the development of ZONEGRAN, nine sudden unexplained deaths occurred among 991 patients with epilepsy receiving ZONEGRAN for whom accurate exposure data are available. This represents an incidence of 7.7 deaths per 1000 patient years. Although this rate exceeds that expected in a healthy population, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with refractory epilepsy not receiving ZONEGRAN (ranging from 0.5 per 1000 patient-years for the general population of patients with epilepsy, to 2–5 per 1000 patient-years for patients with refractory epilepsy; higher incidences range from 9–15 per 1000 patient-years among surgical candidates and surgical failures). Some of the deaths could represent seizure-related deaths in which the seizure was not observed.

Status Epilepticus: Estimates of the incidence of treatment emergent status epilepticus in ZONEGRAN-treated patients are difficult because a standard definition was not employed. Nonetheless, in controlled trials, 1.1% of patients treated with ZONEGRAN had an event labeled as status epilepticus compared to none of the patients treated with placebo. Among patients treated with ZONEGRAN across all epilepsy studies (controlled and uncontrolled), 1.0% of patients had an event reported as status epilepticus.

Creatine Phosphokinase (CPK) Elevation and Pancreatitis: In the post-market setting, the following rare adverse events have been observed (<1:1000):

If patients taking zonisamide develop severe muscle pain

and/or weakness, either in the presence or absence of a fever, markers of muscle damage should be assessed, including serum CPK and aldolase levels. If elevated, in the absence of another obvious cause such as trauma, grand mal seizures, etc., tapering and/or discontinuation of zonisamide should be considered and appropriate treatment initiated.

Patients taking zonisamide that manifest clinical signs and symptoms of pancreatitis should have pancreatic lipase and amylase levels monitored. If pancreatitis is evident, in the absence of another obvious cause, tapering and/or discontinuation of zonisamide should be considered and appropriate treatment initiated.

Information for Patients: Patients should be advised as follows:

1. ZONEGRAN may produce drowsiness, especially at higher doses. Patients should be advised not to drive a car or operate other complex machinery until they have gained experience on ZONEGRAN sufficient to determine whether it affects their performance.
2. Patients should contact their physician immediately if a skin rash develops or seizures worsen.
3. Patients should contact their physician immediately if they develop signs or symptoms, such as sudden back pain, abdominal pain, and/or blood in the urine, that could indicate a kidney stone. Increasing fluid intake and urine output may reduce the risk of stone formation, particularly in those with predisposing risk factors for stones.
4. Patients should contact their physician immediately if a child has been taking ZONEGRAN and is not sweating as usual with or without a fever.
5. Because zonisamide can cause hematological complications, patients should contact their physician immediately if they develop a fever, sore throat, oral ulcers, or easy bruising.
6. As with other AEDs, patients should contact their physician if they intend to become pregnant or are pregnant during ZONEGRAN therapy. Patients should notify their physician if they intend to breast-feed or are breast-feeding an infant.
7. Patients should contact their physician immediately if they develop severe muscle pain and/or weakness.

Laboratory Tests: In several clinical studies, zonisamide was associated with a mean increase in the concentration of serum creatinine and blood urea nitrogen (BUN) of approximately 8% over the baseline measurement. Consideration should be given to monitoring renal function periodically (see PRECAUTIONS, Effect on Renal Function subsection).

Zonisamide was associated with an increase in serum alkaline phosphatase. In the randomized, controlled trials, a mean increase of approximately 7% over baseline was associated with zonisamide compared to a 3% mean increase in placebo-treated patients. These changes were not statistically significant. The clinical relevance of these changes is unknown.

Drug Interactions: Effects of ZONEGRAN on the pharmacokinetics of other antiepilepsy drugs (AEDs): Zonisamide had no appreciable effect on the steady state plasma concentrations of phenytoin, carbamazepine, or valproate during clinical trials. Zonisamide did not inhibit mixed-function liver oxidase enzymes (cytochrome P450), as measured in human liver microsomal preparations, *in vitro*. Zonisamide is not expected to interfere with the metabolism of other drugs that are metabolized by cytochrome P450 isozymes.

Effects of other drugs on ZONEGRAN pharmacokinetics: Drugs that induce liver enzymes increase the metabolism and clearance of zonisamide and decrease its half-life. The half-life of zonisamide following a 400 mg dose in patients concurrently on enzyme-inducing AEDs such as phenytoin, carbamazepine, or phenobarbital was between 27–38 hours; the half-life of zonisamide in patients concurrently on the non-enzyme inducing AED, valproate, was 46 hours. Concurrent medication with drugs that either induce or inhibit CYP3A4 would be expected to alter serum concentrations of zonisamide.

Interaction with cimetidine: Zonisamide single dose pharmacokinetic parameters were not affected by cimetidine (300 mg four times a day for 12 days).

Carcinogenicity, Mutagenesis, Impairment of Fertility: No evidence of carcinogenicity was found in mice or rats following dietary administration of zonisamide for two years at doses of up to 80 mg/kg/day. In mice, this dose is approximately equivalent to the maximum recommended human dose (MRHD) of 400 mg/day on a mg/m² basis. In rats, this dose is 1–2 times the MRHD on a mg/m² basis.

Zonisamide increased mutation frequency in Chinese hamster lung cells in the absence of metabolic activation. Zonisamide was not mutagenic or clastogenic in the Ames test, mouse lymphoma assay, sister chromatid exchange test, and human lymphocyte cytogenetics assay *in vitro*, and the rat bone marrow cytogenetics assay *in vivo*.

Rats treated with zonisamide (20, 60, or 200 mg/kg) before mating and during the initial gestation phase showed signs of reproductive toxicity (decreased corpora lutea, implantations, and live fetuses) at all doses. The low dose in this study is approximately 0.5 times the maximum recommended human dose (MRHD) on a mg/m² basis. The effect of zonisamide on human fertility is unknown.

Pregnancy: Pregnancy Category C (see WARNINGS, Teratogenicity subsection): Zonisamide was teratogenic in mice, rats, and dogs and embryolethal in monkeys when administered during the period of organogenesis. Fetal abnormalities or embryo-fetal deaths occurred in these species at zonisamide dosage and maternal plasma levels similar to or lower than therapeutic levels in humans, indicating that use of this drug in pregnancy entails a significant risk to the fetus. A variety of external, visceral, and skeletal malformations was produced in animals by prenatal exposure to zonisamide. Cardiovascular defects were prominent in both rats and dogs.

Following administration of zonisamide (10, 30, or 60 mg/kg/day) to pregnant dogs during organogenesis, increased incidences of fetal cardiovascular malformations [ventricular

septal defects, cardiomegaly, various valvular and arterial anomalies) were found at doses of 30 mg/kg/day or greater. The low effect dose for malformations produced peak maternal plasma zonisamide levels (25 µg/mL) about 0.5 times the highest plasma levels measured in patients receiving the maximum recommended human dose (MRHD) of 400 mg/day. In dogs, cardiovascular malformations were found in approximately 50% of all fetuses exposed to the high dose, which was associated with maternal plasma levels (44 µg/mL) approximately equal to the highest levels measured in humans receiving the MRHD. Incidences of skeletal malformations were also increased at the high dose, and fetal growth retardation and increased frequencies of skeletal variations were seen at all doses in this study. The low dose produced maternal plasma levels (12 µg/mL) about 0.25 times the highest human levels.

In cynomolgus monkeys, administration of zonisamide (10 or 20 mg/kg/day) to pregnant animals during organogenesis resulted in embryo-fetal deaths at both doses. The possibility that these deaths were due to malformations cannot be ruled out. The lowest embryolethal dose in monkeys was associated with peak maternal plasma zonisamide levels (5 µg/mL) approximately 0.1 times the highest levels measured in patients at the MRHD.

In a mouse embryo-fetal development study, treatment of pregnant animals with zonisamide (125, 250, or 500 mg/kg/day) during the period of organogenesis resulted in increased incidences of fetal malformations (skeletal and/or craniofacial defects) at all doses tested. The low dose in this study is approximately 1.5 times the MRHD on a mg/m² basis. In rats, increased frequencies of malformations (cardiovascular defects) and variations (persistent cords of thymic tissue, decreased skeletal ossification) were observed among the offspring of dams treated with zonisamide (20, 60, or 200 mg/kg/day) throughout organogenesis at all doses. The low effect dose is approximately 0.5 times the MRHD on a mg/m² basis.

Perinatal death was increased among the offspring of rats treated with zonisamide (10, 30, or 60 mg/kg/day) from the latter part of gestation up to weaning at the high dose, or approximately 1.4 times the MRHD on a mg/m² basis. The no effect level of 30 mg/kg/day is approximately 0.7 times the MRHD on a mg/m² basis.

There are no adequate and well-controlled studies in pregnant women. ZONEGRAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of ZONEGRAN on labor and delivery in humans is not known.

Use in Nursing Mothers: It is not known whether zonisamide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from zonisamide, a decision should be made whether to discontinue nursing or to discontinue drug, taking into account the importance of the drug to the mother. ZONEGRAN should be used in nursing mothers only if the benefits outweigh the risks.

Pediatric Use: The safety and effectiveness of ZONEGRAN in children under age 16 have not been established. Cases of oligohydrosis and hyperpyrexia have been reported (see **WARNINGS, Oligohydrosis and Hyperthermia in Pediatric Patients** subsection).

Geriatric Use: Single dose pharmacokinetic parameters are similar in elderly and young healthy volunteers (see **CLINICAL PHARMACOLOGY, Special Populations** subsection in full Prescribing Information). Clinical studies of zonisamide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The most commonly observed adverse events associated with the use of ZONEGRAN in controlled clinical trials that were not seen at an equivalent frequency among placebo-treated patients were somnolence, anorexia, dizziness, headache, nausea, and agitation/irritability.

In controlled clinical trials, 12% of patients receiving ZONEGRAN as adjunctive therapy discontinued due to an adverse event compared to 6% receiving placebo. Approximately 21% of the 1,336 patients with epilepsy who received ZONEGRAN in clinical studies discontinued treatment because of an adverse event. The adverse events most commonly associated with discontinuation were somnolence, fatigue and/or ataxia (6%), anorexia (3%), difficulty concentrating (2%), difficulty with memory, mental slowing, nausea/vomiting (2%), and weight loss (1%). Many of these adverse events were dose-related (see **WARNINGS and PRECAUTIONS**).

Adverse Event Incidence in Controlled Clinical Trials: Table 3 lists treatment-emergent adverse events that occurred in at least 2% of patients treated with ZONEGRAN in controlled clinical trials that were numerically more common in the ZONEGRAN group. In these studies, either ZONEGRAN or placebo was added to the patient's current AED therapy. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures, obtained when ZONEGRAN was added to concurrent AED therapy, cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

Table 3. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials (Events that oc-

curred in at least 2% of ZONEGRAN-treated patients and occurred more frequently in ZONEGRAN-treated than placebo-treated patients)

ZONEGRAN (n=269) PLACEBO (n=230)

BODY AS A WHOLE Headache (10%/8%), Abdominal Pain (6%/3%), Flu Syndrome (4%/3%) **DIGESTIVE** Anorexia (13%/6%), Nausea (9%/6%), Diarrhea (5%/2%), Dyspepsia (3%/1%), Constipation (2%/1%), Dry Mouth (2%/1%) **HEMATOLOGIC AND LYMPHATIC** Erythema (2%/1%) **METABOLIC AND NUTRITIONAL** Weight Loss (3%/2%) **NEUROUS SYSTEM** Dizziness (13%/7%), Ataxia (6%/1%), Nystagmus (4%/2%), Paresthesia (4%/1%) **NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-ALTERED COGNITIVE FUNCTION** Confusion (6%/3%), Difficulty Concentrating (6%/2%), Difficulty with Memory (6%/2%), Mental Slowing (4%/2%) **NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-BEHAVIORAL ABNORMALITIES (NON-PSYCHOSIS-RELATED)** Agitation/Irritability (9%/4%), Depression (6%/3%), Insomnia (6%/3%), Anxiety (3%/2%), Nervousness (2%/1%) **NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-BEHAVIORAL ABNORMALITIES (PSYCHOSIS-RELATED)** Schizophrenic/Schizophreniform Behavior (2%/0%) **NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-CNS DEPRESSION** Somnolence (17%/7%), Fatigue (8%/6%), Tiredness (7%/5%) **NEUROPSYCHIATRIC AND COGNITIVE DYSFUNCTION-SPEECH AND LANGUAGE ABNORMALITIES** Speech Abnormalities (5%/2%), Difficulties in Verbal Expression (2%/<1%) **RESPIRATORY** Rhinitis (2%/1%) **SKIN AND APPENDAGES** Rash (3%/2%) **SPECIAL SENSES** Diplopia (6%/3%), Taste Perversion (2%/0%)

Other Adverse Events Observed During Clinical Trials: ZONEGRAN has been administered to 1,598 individuals during all clinical trials, only some of which were placebo-controlled. During these trials, all events were recorded by the investigators using their own terms. To provide a useful estimate of the proportion of individuals having adverse events, similar events have been grouped into a smaller number of standardized categories using a modified COSTART dictionary. The frequencies represent the proportion of the 1,598 individuals exposed to ZONEGRAN who experienced an event on at least one occasion. All events are included except those already listed in the previous table or discussed in **WARNINGS** or **PRECAUTIONS**, trivial events, those too general to be informative, and those not reasonably associated with ZONEGRAN.

Events are further classified within each category and listed in order of decreasing frequency as follows: **frequent** occurring in at least 1:100 patient; **infrequent** occurring in 1:100 to 1:1000 patients; **rare** occurring in fewer than 1:1000 patients.

Body as a Whole: *Frequent:* Accidental injury, asthenia. *Infrequent:* Chest pain, flank pain, malaise, allergic reaction, face edema, neck rigidity. *Rare:* Lupus erythematosus.

Cardiovascular: *Infrequent:* Palpitation, tachycardia, vascular insufficiency, hypotension, hypertension, thrombophlebitis, syncope, bradycardia. *Rare:* Atrial fibrillation, heart failure, pulmonary embolus, ventricular extrasystoles.

Digestive: *Frequent:* Vomiting. *Infrequent:* Flatulence, gingivitis, gum hyperplasia, gastritis, gastroenteritis, stomatitis, cholelithiasis, glossitis, melena, rectal hemorrhage, ulcerative stomatitis, gastro-duodenal ulcer, dysphagia, gum hemorrhage. *Rare:* Cholangitis, hematemesis, cholecystitis, cholestatic jaundice, colitis, duodenitis, esophagitis, fecal incontinence, mouth ulceration.

Hematologic and Lymphatic: *Infrequent:* Leukopenia, anemia, immunodeficiency, lymphadenopathy. *Rare:* Thrombocytopenia, microcytic anemia, petechia.

Metabolic and Nutritional: *Infrequent:* Peripheral edema, weight gain, edema, thirst, dehydration. *Rare:* Hypoglycemia, hyponatremia, lactic dehydrogenase increased, SGOT increased, SGPT increased.

Musculoskeletal: *Infrequent:* Leg cramps, myalgia, myasthenia, arthralgia, arthritis.

Nervous System: *Frequent:* Tremor, convulsion, abnormal gait, hyperesthesia, incoordination. *Infrequent:* Hypertonia, twitching, abnormal dreams, vertigo, libido decreased, neuropathy, hyperkinesia, movement disorder, dysarthria, cerebrovascular accident, hypotonia, peripheral neuritis, parathesia, reflexes increased. *Rare:* Circumoral paresthesia, dyskinesia, dystonia, encephalopathy, facial paralysis, hypokinesia, hyperesthesia, myoclonus, oculogyric crisis.

Behavioral Abnormalities - Non-Psychosis-Related: *Infrequent:* Euphoria.

Respiratory: *Frequent:* Pharyngitis, cough increased. *Infrequent:* Dyspnea. *Rare:* Apnea, hemoptysis.

Skin and Appendages: *Frequent:* Pruritus. *Infrequent:* Maculopapular rash, acne, alopecia, dry skin, sweating, eczema, urticaria, hirsutism, pustular rash, vesiculobullous rash.

Special Senses: *Frequent:* Amblyopia, tinnitus. *Infrequent:* Conjunctivitis, parosmia, deafness, visual field defect, glaucoma. *Rare:* Photophobia, iritis.

Urogenital: *Infrequent:* Urinary frequency, dysuria, urinary incontinence, hematuria, impotence, urinary retention, urinary urgency, amenorrhea, polyuria, nocturia. *Rare:* Albuminuria, enuresis, bladder pain, bladder calculus, gynecomastia, mastitis, menorrhagia.

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