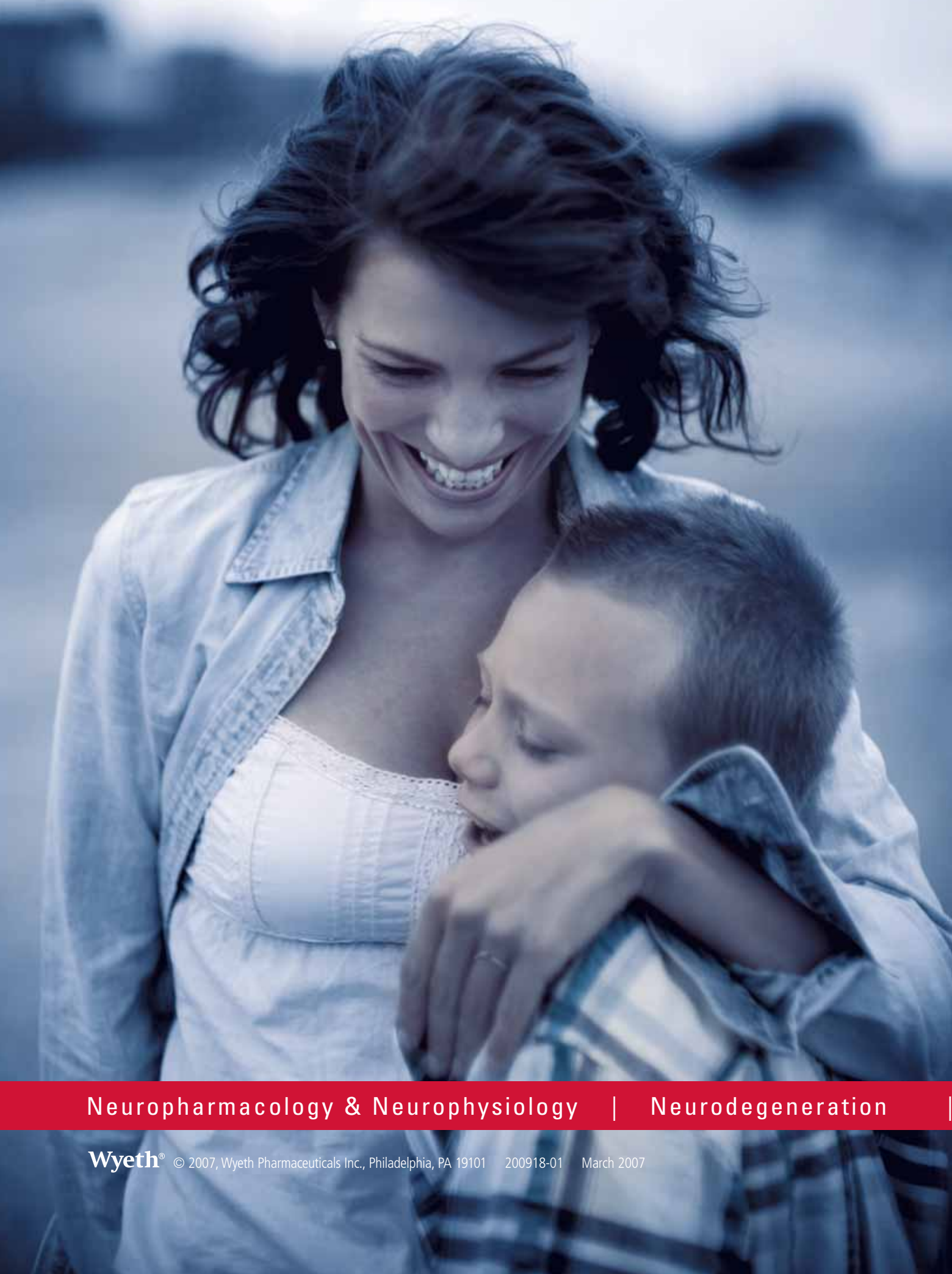

Neuropharmacology & Neurophysiology | Neurodegeneration

She couldn't imagine her future without depression. But we can.

Wyeth Neuroscience believes that everyone deserves a healthier tomorrow. That's why Wyeth is building one of the world's leading pipelines focused on such challenging disease areas as depression, schizophrenia, bipolar disorder, Alzheimer's disease, stroke, and pain. Our passion for research and development has produced innovative therapies that make a real difference for millions of patients. Already recognized as having a top 10 pipeline, Wyeth continues to develop new drugs that we hope will change the future of health care. Because every discovery brings new hope for patients everywhere.

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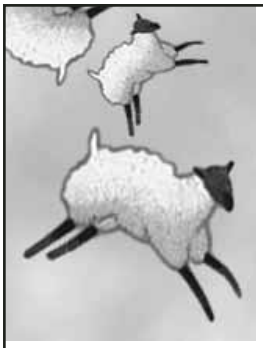

APA 2007 Annual Meeting sponsored by the American Psychiatric Association

Making Every Sheep Count:

Evidence-Based Approaches to Treating Insomnia

Sunday, May 20, 2007

1:00 – 1:30 PM Lunch

1:30 – 4:30 PM Symposium

Marriott San Diego Hotel & Marina
Marina Ballroom, South Tower, Level 3
333 West Harbor Drive
San Diego, California

Educational Objectives

At the end of this educational activity participants should be able to

1. Summarize the neural circuitry and physiological regulation of sleep, wakefulness, and circadian rhythms in humans. Relate the neurobiology of sleep to insomnia and its daytime consequences
2. Describe the emerging evidence regarding interactions between sleep, circadian rhythms, and psychiatric disorders
3. Explain the biological basis for nonpharmacologic treatments of insomnia and nightmare disorders, and apply the basic elements of these treatments in clinical practice
4. Discuss new developments and new treatment targets for pharmacologic management of insomnia

Accreditation

The American Psychiatric Association (APA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The APA designates this educational activity of a maxiumum of *3 AMA PRA category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activty.

Attendees must be registered for the APA Annual Meeting to attend this symposium. Seating is limited and will be based on first-come, first-served. For more information about the meeting, please visit the APA web site at www.psych.org or contact the APA toll free at 1-888-357-7924 (within the US or Canada) or 703-907-7300.

Registered conference participants and registered guests may attend an industry supported symposium at the APA meeting.

Sponsored by the American Psychiatric Association
Supported by an educational grant from Takeda Pharmaceuticals North America.

Agenda

1:30–1:40 PM **Opening Remarks**
Daniel J. Buysse, MD–Chairman
University of Pittsburgh School of Medicine

1:40–2:10 PM **The Clinical Neuroscience of Sleep and Insomnia**
Daniel J. Buysse, MD

2:10–2:40 PM **Comorbidity Between Insomnia and Psychiatric Illness**
Meera Narasimhan, MD
University of South Carolina School of Medicine

2:40–3:10 PM **Novel Pharmacological Targets for the Management of Insomnia**
Ruth M. Benca, MD, PhD
University of Wisconsin-Madison

3:10–3:40 PM **Innovative Behavioral Approaches for Treating Insomnia and Comorbid Psychiatric Illness**
Karl Doghramji, MD
Thomas Jefferson University

3:40–4:25 PM **Panel Discussion**
Faculty Panel

APA 2007 Annual Meeting Sponsored by the American Psychiatric Association

Weighing the Risks and Benefits of Atypical Antipsychotics:

Can We Have Our Cake and Eat It Too?

Sunday, May 20, 2007

Dinner: 6:30–7:00 PM
Symposium: 7:00–10:00 PM

Manchester Grand Hyatt San Diego
Douglas Pavilion C/D
One Market Place
San Diego, California

Agenda

7:00 PM **Opening Remarks**
Henry A. Nasrallah, MD – Chairman • University of Cincinnati College of Medicine

7:05 **High Morbidity and Mortality in Schizophrenia and Bipolar Disorder: What, Why, and How?***
Quinton E. Moss, MD • University of Cincinnati College of Medicine

7:35 **Metabolic Complications in the Context of Antipsychotic Effectiveness: Lessons from the CATIE Schizophrenia Trial***
Donald C. Goff, MD • Harvard Medical School

8:05 **The Dual Health Jeopardy in Schizophrenia: Highly Prevalent Metabolic Disorders and Low Access to Medical Treatment***
Henry A. Nasrallah, MD

8:35 **Lessons From ATP III, the ADA, and the APA Workgroup on Antipsychotics and Metabolic Risk***
John W. Newcomer, MD • Washington University School of Medicine

9:05 **Patient, Provider, and System Approches to Reducing Risk of Poor Health in Patients Receiving Antipsychotics***
Lisa B. Dixon, MD, MPH • University of Maryland School of Medicine, VA Capitol Health Care Network MIRECC

9:35 **Question and Answer**

10:00 **Closing Remarks**

*Each presentation will include 5 minutes for audience questions.

Educational Objectives

At the end of this educational activity participants should be able to

1. Review the epidemiological studies demonstrating high rates of morbidity and mortality in schizophrenia and bipolar disorder patients.
2. Discuss the high prevalence of the metabolic syndrome in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) sample and the low rates of treatment for it.
3. Compare and contrast the metabolic profiles of antipsychotics in the CATIE study.
4. Identify potential patient, provider and system level interventions to improve metabolic outcomes among patients treated with antipsychotic medications.

Accreditation/Support

The American Psychiatric Association (APA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The APA designates this educational activity of a maxiumum of *3 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activty.

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Registered conference participants and registered guests may attend an industry supported symposium at the APA meeting.

Co-supported by an educational grant from

Bristol-Myers Squibb Otsuka America Pharmaceutical, Inc.

Dark Horizons: Depression and Cognitive Impairment

Sunday, May 20, 2007
Breakfast: 7:30 - 8:00 AM
Scientific Program: 8:00 - 11:00 AM

Held at the APA 2007 Annual Meeting
Manchester Grand Hyatt
Manchester Ballroom, Second Level
San Diego, California

Agenda

7:30 AM **Breakfast**

8:00 **Welcome and Introduction**
Steven P. Roose, MD – Chairman
Columbia University, College of Physicians and Surgeons
New York State Psychiatric Institute

8:10 **The Epidemiology and Genetic Studies of Depression and Memory***
Richard Mayeux, MD, MSc
Columbia University, College of Physicians and Surgeons
New York State Psychiatric Institute

8:40 **The Biology of Depression and Dementia***
Gary W. Small, MD
David Geffen School of Medicine at UCLA

9:10 **Vascular Depression and Vascular Dementia***
K. Ranga R. Krishnan, MB, ChB
Duke University Medical Center

9:40 **The Course of Treatment for Patients With Questionable Dementia***
D.P. Devanand, MD
Columbia University, College of Physicians and Surgeons
New York State Psychiatric Institute

10:10 **The Course of Treatment for Patients With Depression and Mild Cognitive Impairment***
Roy Hamilton, MD, MS
University of Pennsylvania

10:40 **Panel Discussion and Q & A Session**

11:00 **Conclusion**

*Each presentation will include 5 minutes for audience questions.

The American Psychiatric Association (APA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The APA designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Educational Objectives:

- Evaluate the data that older adults with depressive symptoms are at a higher risk for the development of dementia.
- Identify the neurochemical and neurobiologic changes that occur in patients with recurrent depression and how these changes may influence the development of dementia.
- Review the concept of vascular depression and poststroke depression and discuss whether patients with these disorders progress to vascular dementia.
- Understand the phenomenology and course of treatment for patients with mild cognitive impairment with no depressive symptoms to determine the phenomenologic fate of this group.
- Identify treatment options available to patients with combined mood and memory disorders, particularly to review whether effective treatments can forestall the devastating impact of these illnesses in a late-life population.

Sponsored by the American Psychiatric Association

Supported by an educational grant from Forest Pharmaceuticals, Inc.

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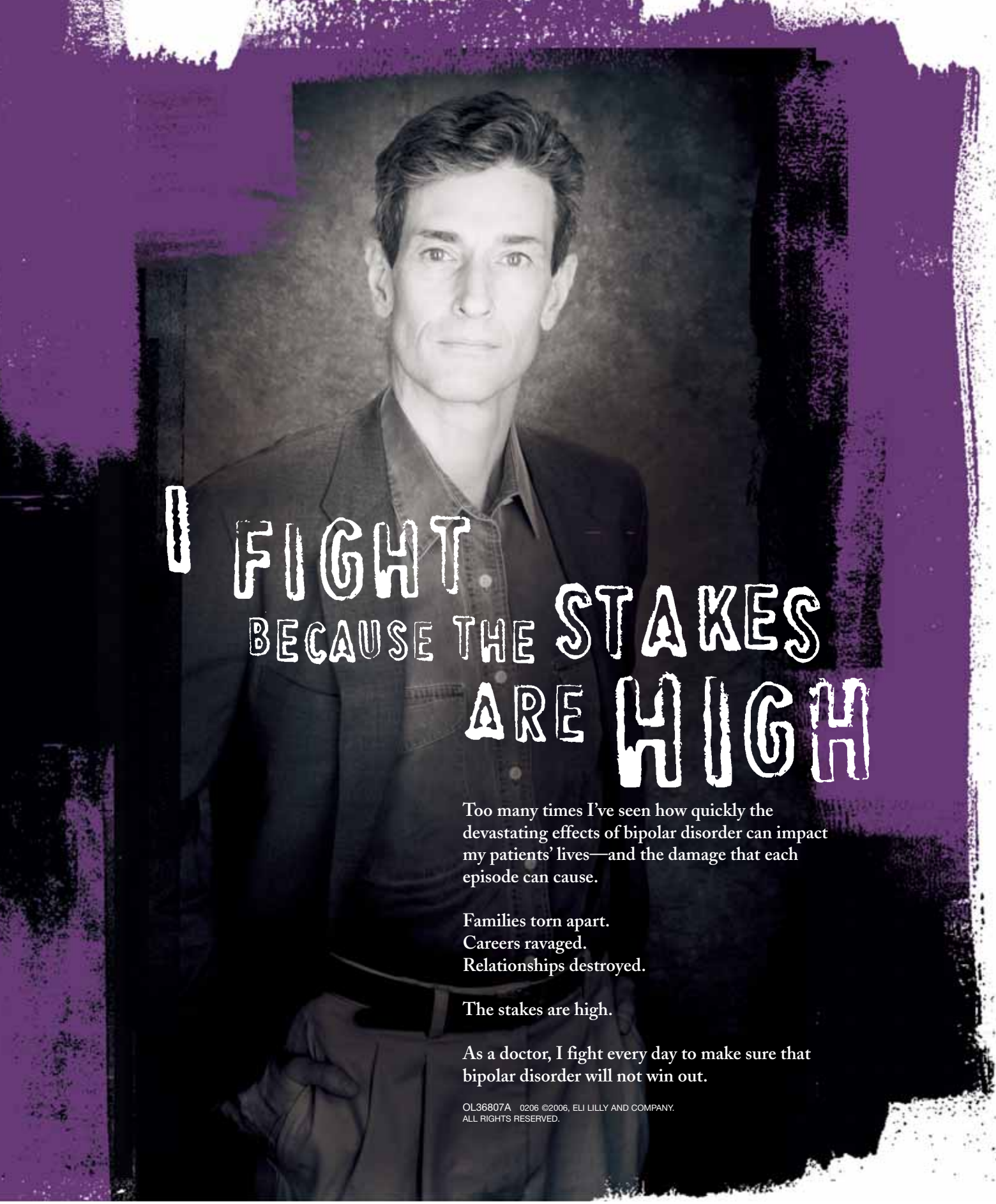

I FIGHT BECAUSE THE STAKES ARE HIGH

Too many times I've seen how quickly the devastating effects of bipolar disorder can impact my patients' lives—and the damage that each episode can cause.

Families torn apart.
Careers ravaged.
Relationships destroyed.

The stakes are high.

As a doctor, I fight every day to make sure that bipolar disorder will not win out.

Lilly

PRESENTED AT THE APA 2007 ANNUAL MEETING IN SAN DIEGO, CA

Tuesday, May 22, 2007 ◆ 7:00–10:00 pm
San Diego Convention Center Ballroom 20, Upper Level

Cigarette Smoking, Smoking Cessation, AND Psychiatric Illness

PROGRAM AGENDA

6:30–7:00 pm
Dinner

7:00–7:10 pm
Introduction
Alexander H. Glassman, MD (Chair)
Columbia University College of Physicians and Surgeons
New York State Psychiatric Institute

7:10–7:35 pm
Reward Systems Underlying Motivation and Addiction
Peter W. Kalivas, PhD
Medical University of South Carolina

7:35–8:00 pm
Animal Modeling and Integrative Neurocircuitry of Addiction Vulnerability in Mental Illness
R. Andrew Chambers, MD
Indiana University School of Medicine

8:00–8:25 pm
Pharmacotherapies for Smoking Cessation
Cheryl Oncken, MD, MPH
University of Connecticut Health Center

8:25–8:50 pm
What Makes Smoking Cessation Unique in Patients with a History of Depression?
Alexander H. Glassman, MD
Columbia University College of Physicians and Surgeons
New York State Psychiatric Institute

8:50–9:15 pm
Pharmacological Treatment of Nicotine Dependence in Schizophrenia: The Devil Is in the Details
Tony P. George, MD, FRCPC
University of Toronto
Centre for Addiction and Mental Health

9:15–10:00 pm
Panel Discussion/Q&A

LEARNING OBJECTIVES

At the conclusion of this symposium, the participant should be able to:

- Recognize the unique risks of cigarette smoking for patients with psychiatric illness.
- Discuss common neurobiology underlying all addictions.
- Compare and contrast smoking addiction in patients with depression and schizophrenia.
- Outline tools and treatments for smoking cessation in patients with and without psychiatric illness.

Supported by an educational grant from

Pfizer

Sponsored by the American Psychiatric Association

REGISTRATION

Attendees must be registered for the APA Annual Meeting to attend this symposium. Seating is limited and will be based on first-come, first-served. For more information about the meeting, please visit the APA website at www.psych.org or contact the APA toll-free at 1-888-357-7924 (within the U.S. or Canada) or 703-907-7300.

CREDIT DESIGNATION

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ACCREDITATION STATEMENT

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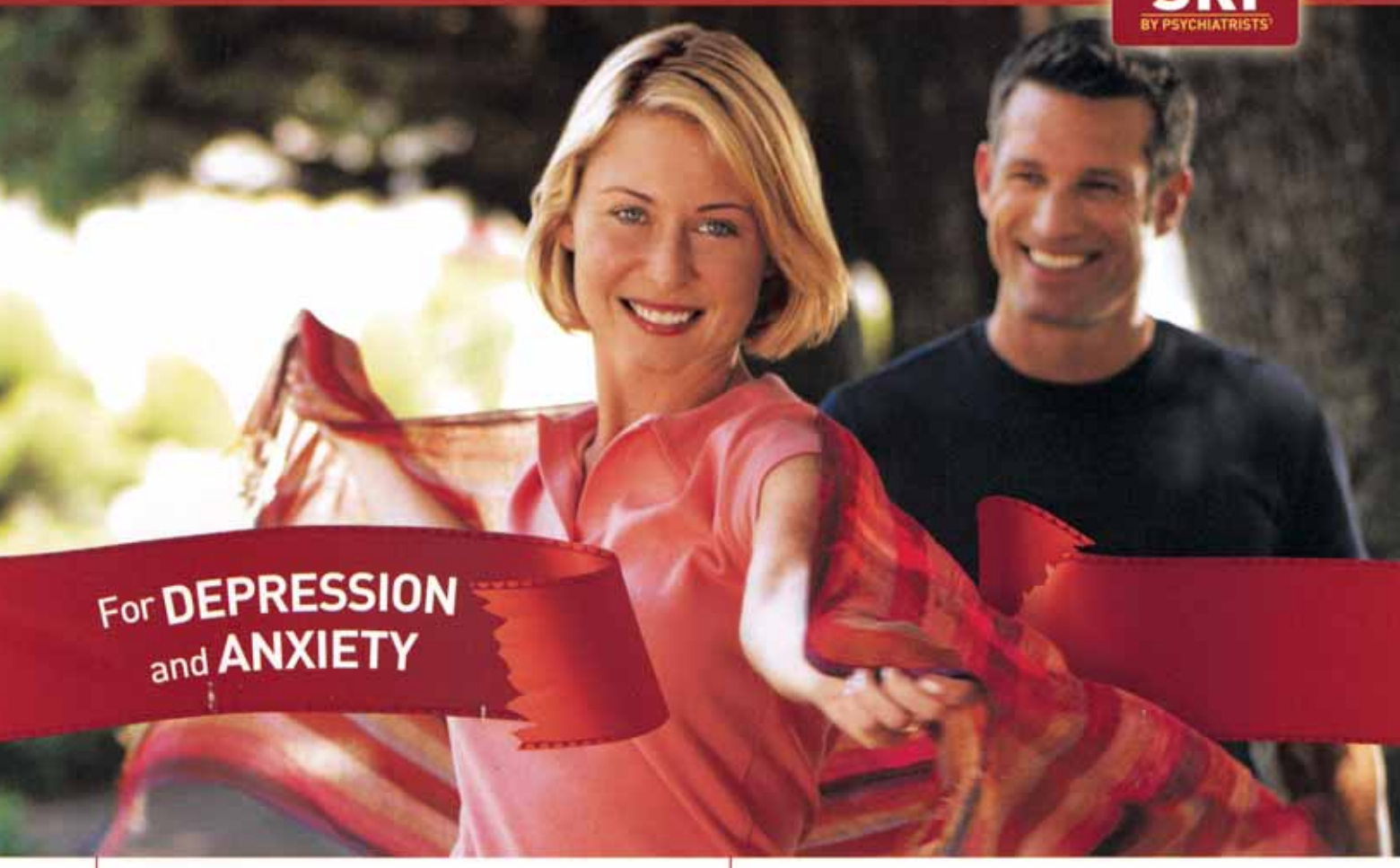
A POWERFUL SSRI that's well tolerated

#1 PRESCRIBED SRI BY PSYCHIATRISTS[1]



UP TO 90% of depressed patients present with symptoms of anxiety[2]

PROVEN EFFICACY for Major Depressive Disorder and Generalized Anxiety Disorder[3]

Lexapro escitalopram oxalate

POWER TO ENJOY LIFE™

IMPORTANT SAFETY INFORMATION – Depression is a serious condition that can lead to suicidal thoughts and behavior. Antidepressants increased the risk of suicidal thinking and behavior (2% to 4%) in short-term studies of 9 antidepressant drugs in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Patients started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially at the beginning of therapy or at the time of dose changes. This risk may persist until significant remission occurs. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients.

Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs), pimozide (see DRUG INTERACTIONS – Pimozide and Celexa), or in patients with hypersensitivity to escitalopram oxalate. As with other SSRIs, caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with Lexapro. As with other psychotropic drugs that interfere with serotonin reuptake, patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation. The most common adverse events with Lexapro versus placebo (approximately 5% or greater and approximately 2x placebo) were nausea, insomnia, ejaculation disorder, somnolence, increased sweating, fatigue, decreased libido, and anorgasmia.

References: **1.** IMS National Prescription Audit. Twelve-month rolling average. November 2006. **2.** Sadock BJ, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry.* 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins;2003:552. **3.** LEXAPRO [package insert]. St Louis, Mo: Forest Pharmaceuticals, Inc.; 2006.

Please see brief summary of prescribing information for LEXAPRO on following page.

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

Rx Only

Brief Summary: For complete details, please see full prescribing information for Lexapro.

Suicidality in Children and Adolescents Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use) Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

CONTRAINDICATIONS Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**). Concomitant use in patients taking pimozide is contraindicated (see **Drug Interactions – Pimozide and Celexa**). Lexapro is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in Lexapro. **WARNINGS WARNINGS-Clinical Worsening and Suicide Risk Clinical Worsening and Suicide Risk** Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. **All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits. Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION—Discontinuation of Treatment with Lexapro, in full prescribing information for a description of the risks of discontinuation of Lexapro). Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Lexapro is not approved for use in treating bipolar depression. **Potential for Interaction with Monoamine Oxidase Inhibitors In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.** ***Serotonin Syndrome:*** The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Lexapro treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The concomitant use of Lexapro with MAOIs intended to treat depression is contraindicated (see **CONTRAINDICATIONS** and **WARNINGS - Potential for Interaction with Monoamine Oxidase Inhibitors.**) If concomitant treatment of Lexapro with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **PRECAUTIONS - Drug Interactions**).The concomitant use of Lexapro with serotonin precursors (such as tryptophan) is not recommended (see **PRECAUTIONS - Drug Interactions**). **PRECAUTIONS** Information for Patients Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of Lexapro and triptans, tramadol or other serotonergic agents. **Drug Interactions** ***Serotonergic Drugs:*** Based on the mechanism of action of SNRIs and SSRIs including Lexapro, and the potential for serotonin syndrome, caution is advised when Lexapro is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see **WARNINGS - Serotonin Syndrome**). The concomitant use of Lexapro with other SSRIs, SNRIs or tryptophan is not recommended (see **PRECAUTIONS - Drug Interactions**). ***Triptans:*** There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Lexapro with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS - Serotonin Syndrome**). **General** Discontinuation of Treatment with Lexapro During marketing of Lexapro and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Lexapro. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see **DOSAGE AND ADMINISTRATION** in full prescribing information). Abnormal Bleeding Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see **Drug Interactions**). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Lexapro with NSAIDs, aspirin, or other drugs that affect coagulation. Hyponatremia Cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with Lexapro treatment. All patients with these events have recovered with discontinuation of escitalopram and/or medical intervention. Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder. Activation of Mania/Hypomania In placebo-controlled trials of Lexapro in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Lexapro and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Lexapro treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro should be used cautiously in patients with a history of mania. Seizures Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Lexapro, cases of convulsion have been reported in association with Lexapro treatment. Like other drugs effective in the treatment of major depressive disorder, Lexapro should be introduced with care in patients with a history of seizure disorder. Interference with Cognitive and Motor Performance In a study in normal volunteers, Lexapro 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. Use in Patients with Concomitant Illness Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day (see **DOSAGE AND ADMINISTRATION** in full prescribing information). Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Lexapro, however, it should be used with caution in such patients (see **DOSAGE AND ADMINISTRATION** in full prescribing information). **Drug Interactions** CNS Drugs - Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs. Alcohol - Although Lexapro did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Lexapro is not recommended. Monoamine Oxidase Inhibitors (MAOIs) - See **CONTRAINDICATIONS** and **WARNINGS**. **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with Lexapro. Cimetidine - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Digoxin - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. Lithium - Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Lexapro and lithium are coadministered. Pimozide and Celexa - In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known. Sumatriptan - There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised. Theophylline - Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. Warfarin - Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. Carbamazepine - Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered. Triazolam - Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. Ketoconazole - Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. Ritonavir - Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram. CYP3A4 and -2C19 Inhibitors - *In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance. Drugs Metabolized by Cytochrome P4502D6 - *In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6. Metoprolol - Administration of 20 mg/day Lexapro for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Lexapro and metoprolol had no clinically significant effects on blood pressure or heart rate. Electroconvulsive Therapy (ECT) - There are no clinical studies of the combined use of ECT and escitalopram. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenesis Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown. Mutagenesis Racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays. Impairment of Fertility When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥ 32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day. **Pregnancy-Nonteratogenic Effects** Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS**). Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION** in full prescribing information). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **Labor and Delivery** The effect of Lexapro on labor and delivery in humans is unknown. **Nursing Mothers** Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and, in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or Lexapro therapy should take into account the risks of citalopram exposure for the infant and the benefits of Lexapro treatment for the mother. **Pediatric Use** Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS—Clinical Worsening and Suicide Risk**). One placebo-controlled trial in 264 pediatric patients with MDD has been conducted with Lexapro, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Lexapro in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use** Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Lexapro in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out. In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged (see **CLINICAL PHARMACOLOGY**). 10 mg/day is the recommended dose for elderly patients (see **DOSAGE AND ADMINISTRATION** in full prescribing information). Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out. **ADVERSE REACTIONS** Adverse event information for Lexapro was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Lexapro in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials. 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 tabulations that follow, standard World Health Organization (WHO) 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. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Associated with Discontinuation of Treatment Major Depressive Disorder** Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder** Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Events in Placebo-Controlled Clinical Trials Major Depressive Disorder** Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures can not 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. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see **TABLE 1**). **TABLE 1: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder* [Lexapro (N=715) and Placebo (N=592)]: Autonomic Nervous System Disorders:** Dry Mouth (6% and 5%); Sweating Increased (5% and 2%). **Central & Peripheral Nervous System Disorders:** Dizziness (5% and 3%). **Gastrointestinal Disorders:** Nausea (15% and 7%); Diarrhea (8% and 5%); Constipation (3% and 1%); Indigestion (3% and 1%); Abdominal Pain (2% and 1%). **General:** Influenza-like Symptoms (5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1 %); Libido Decreased (3% and 1%). **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder[1,2] (9% and <1%); Impotence[2] (3% and <1%); Anorgasmia[3] (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=225 Lexapro; N=188 placebo). [3]Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder** Table 2 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see **TABLE 2**). **TABLE 2: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* [Lexapro (N=429) and Placebo (N=427)]: Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder[1,2] (14% and 2%); Anorgasmia[3] (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=182 Lexapro; N=195 placebo). [3]Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 3 shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group.**TABLE 3: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125)]: Insomnia** (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%).*Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 4 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 4: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials** [In Males Only: **Lexapro** (N=407) **and Placebo** (N=383)]: Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). [In Females Only: **Lexapro** (N=737) **and Placebo** (N=636)]: Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 1 & 2, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, 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 1/1000 patients. Cardiovascular - *Frequent:* palpitation, hypertension. *Infrequent:* bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - *Frequent:* light-headed feeling, migraine. *Infrequent:* tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - *Frequent:* heartburn, abdominal cramp, gastroenteritis. *Infrequent:* gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - *Frequent:* allergy, pain in limb, fever, hot flushes, chest pain. *Infrequent:* edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - *Infrequent:* bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - *Frequent:* increased weight. *Infrequent:* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - *Frequent:* arthralgia, myalgia. *Infrequent:* jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - *Frequent:* appetite increased, lethargy, irritability, concentration impaired. *Infrequent:* jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female* - *Frequent:* menstrual cramps, menstrual disorder. *Infrequent:* menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only: N= 905 Respiratory System Disorders - *Frequent:* bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. *Infrequent:* asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - *Frequent:* rash. *Infrequent:* pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - *Frequent:* vision blurred, tinnitus. *Infrequent:* taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - *Frequent:* urinary frequency, urinary tract infection. *Infrequent:* urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, prolactinemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

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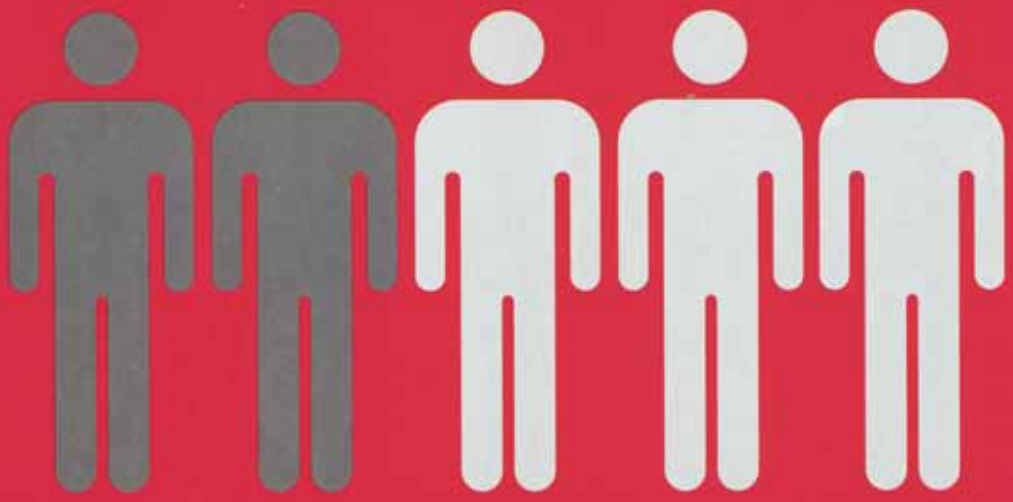

41% of all patients had the metabolic syndrome at baseline in the landmark CATIE schizophrenia study.[2]

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References: 1. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res.* 2005;80:45-53. 2. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res.* 2005;80:19-32.

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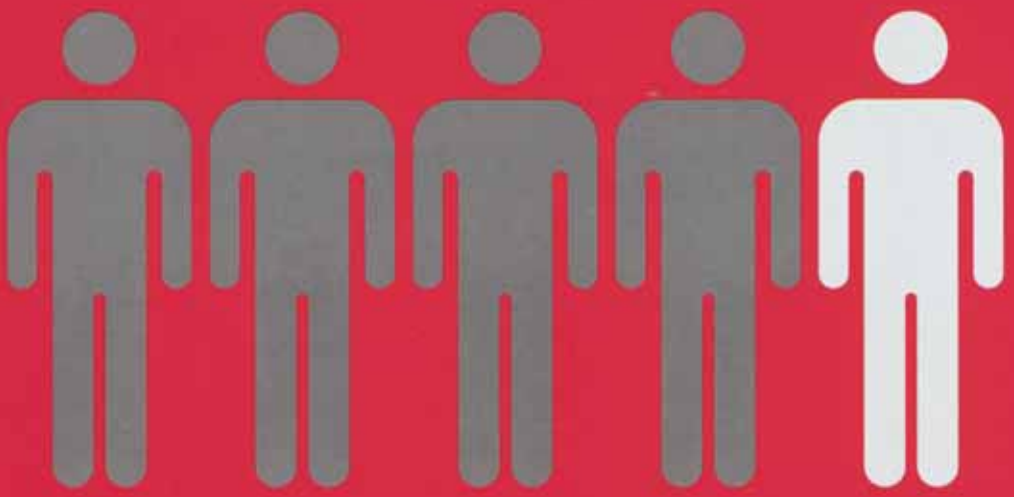

13% of patients had diabetes in the landmark CATIE schizophrenia study at baseline—4 times more common than in the general population.[1]

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PROGRAM AGENDA

1:00 p.m. **Lunch**

1:30 p.m. **Introduction**
Charles B. Nemeroff, MD, PhD (Chair)
Emory University School of Medicine

1:45 p.m. **Mechanism of Action of Vagus Nerve Stimulation (VNS)**
Charles B. Nemeroff, MD, PhD
Emory University School of Medicine

2:15 p.m. **Assessing the Efficacy of VNS in Patients with TRD**
Paul Holtzheimer, MD
Emory University School of Medicine

2:45 p.m. **Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) and Magnetic Seizure Therapy (MST)**
Thomas E. Schlaepfer, MD
University Hospital Bonn
The Johns Hopkins University School of Medicine

3:15 p.m. **Mechanism of Action and Efficacy of Deep Brain Stimulation**
Helen Mayberg, MD
Emory University School of Medicine

3:45 p.m. **Panel Discussion/Q&A**

4:30 p.m. **Conclusion**

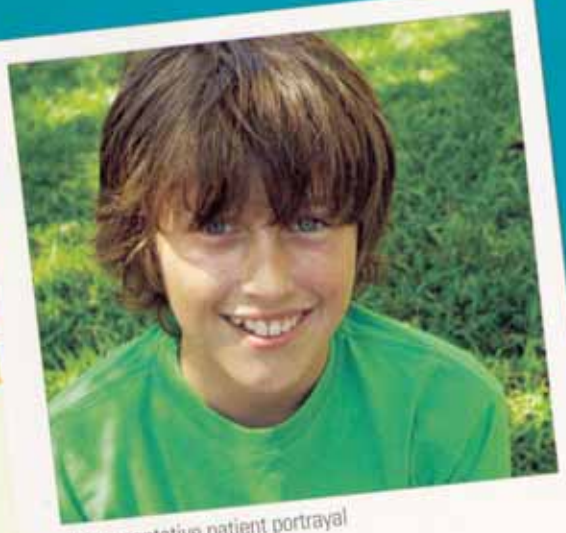
LEARNING OBJECTIVES

At the conclusion of this symposium, the participant should be able to:

1. Identify criteria used to recognize patients with treatment-resistant depression (TRD).
2. Compare and contrast somatic interventions for TRD.
3. Recognize the neurobiological substrates of investigational treatments for refractory depression.

For the treatment of attention deficit hyperactivity disorder (ADHD)

CONCERTA® CAN MAKE A DIFFERENCE



Representative patient portrayal

Meet Matthew, age 12, who has ADHD Combined Type with comorbid ODD*

- Doesn't finish tests or schoolwork
- Forgets to do homework and chores
- Argues with teachers and parents

*ODD=Oppositional Defiant Disorder; CD=Conduct Disorder.

Consider CONCERTA® to give Matthew the help he needs

- Reduces ADHD symptoms in children with ADHD and ODD/CD* as well as in patients with ADHD alone[1]
- Improves academic performance and classroom behavior in children with ADHD[2]
- Significantly reduces ADHD symptoms and conflict with family members in adolescents with ADHD[3]

Important Safety Information

CONCERTA® is indicated for the treatment of ADHD in children and adolescents. CONCERTA® should not be taken by patients with: significant anxiety, tension, or agitation; allergies to methylphenidate or other ingredients in CONCERTA®; glaucoma; Tourette's syndrome, tics, or family history of Tourette's syndrome; current/recent use of monoamine oxidase inhibitors (MAOIs). Children under 6 years of age should not take CONCERTA®. Abuse of methylphenidate may lead to dependence.

Use with caution in patients with psychosis, bipolar disorder, history of seizures/EEG abnormalities, and hypertension. CONCERTA® should not be used in patients with pre-existing severe gastrointestinal narrowing, known structural cardiac abnormalities, or other serious heart problems. Stimulants may cause new psychotic or manic symptoms; discontinuation of treatment may be appropriate. Aggressive behavior or hostility should be monitored in patients beginning treatment. Methylphenidate may produce difficulties with accommodation and blurring of vision. Hematologic monitoring is advised during prolonged therapy.

The most common adverse events reported in children aged 6 to 12 years receiving up to 54 mg were headache (14%), upper respiratory tract infection (8%), and abdominal pain (7%). The most common adverse events reported in adolescents receiving up to 72 mg were headache (9%), accidental injury (6%), and insomnia (5%).

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

For more information, call **1-888-440-7903** or visit **www.concerta.net**

ONCE-DAILY

CONCERTA®

methylphenidate HCl

Extended-release tablets: 18 mg, 27 mg, 36 mg, 54 mg

Delivering results that matter

CON07-034

Expires 6/08

CONCERTA® ℞

(methylphenidate HCl) Extended-release Tablets

BRIEF SUMMARY: Please see full prescribing information.

DESCRIPTION

CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect.

CONTRAINDICATIONS

Agitation: CONCERTA® is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

Hypersensitivity to Methylphenidate: CONCERTA® is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product.

Glaucoma: CONCERTA® is contraindicated in patients with glaucoma.

Tics: CONCERTA® is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome (see ADVERSE REACTIONS).

Monoamine Oxidase Inhibitors: CONCERTA® is contraindicated during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO-inhibitor (hypertensive crises may result) (see PRECAUTIONS, Drug Interactions).

WARNINGS

Serious Cardiovascular Events: Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults: Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and other Cardiovascular Conditions: Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm) (see Adverse Reactions-Hypertension), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications: Children, adolescents, or adults who are being considered for treatment with stimulant medications, should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events: Pre-Existing Psychosis: Administration of stimulants may exacerbate symptoms of behavior and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness: Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms: Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression: Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth: Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treated groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures: There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance: Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Potential for Gastrointestinal Obstruction: Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients).

Use in Children Under Six Years of Age: CONCERTA® should not be used in children under six years, since safety and efficacy in this age group have not been established.

DRUG DEPENDENCE

CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

PRECAUTIONS

Hematologic Monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

Information for Patients: Patients should be informed that CONCERTA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Drug Interactions: CONCERTA® should not be used in patients being treated (currently or within the proceeding 2 weeks) with MAO inhibitors (see CONTRAINDICATIONS, Monoamine Oxidase Inhibitors). Because of possible increases in blood pressure, CONCERTA® should be used cautiously with vasopressor agents. Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate. Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown. Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate. Methylphenidate was not mutagenic in the in vitro Ames reverse mutation assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative in vivo in males and females in the mouse bone marrow micronucleus assay. Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively.

Pregnancy: Teratogenic Effects: ***Pregnancy Category C:*** Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m² basis, respectively. A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m² basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPA in pregnant rats was 2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC. The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. CONCERTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CONCERTA® is administered to a nursing woman.

Pediatric Use: The safety and efficacy of CONCERTA® in children under 6 years old have not been established. Long-term effects of methylphenidate in children have not been well established (see WARNINGS).

ADVERSE REACTIONS

The development program for CONCERTA® included exposures in a total of 2121 participants in clinical trials (1787 patients, 324 healthy adult subjects). These participants received CONCERTA® 18, 36, 54, and/or 72 mg/day. Children, adolescents, and adults with ADHD were evaluated in four controlled clinical studies, three open-label clinical studies and two clinical pharmacology studies. 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. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings in Clinical Trials with CONCERTA®: Adverse Events Associated with Discontinuation of Treatment: In the 4-week placebo-controlled, parallel-group trial in children (Study 3), one CONCERTA®-treated patient (0.9%; 1/106) and one placebo-treated patient (1.0%; 1/99) discontinued due to an adverse event (sadness and increase in tics, respectively). In the 2-week placebo-controlled phase of a trial in adolescents (Study 4), no CONCERTA®-treated patients (0%; 0/87) and 1 placebo-treated patient (1.1%; 1/90) discontinued due to an adverse event (increased mood irritability). In the two open-label, long-term safety trials (Studies 5 and 6; one 24-month study in children aged 6 to 13 and one 9-month study in child, adolescent and adult patients treated with CONCERTA®), 6.7% (101/1514) of patients discontinued due to adverse events. These events with an incidence of >0.5% included insomnia (1.5%), twitching (1.0%), nervousness (0.7%), emotional lability (0.7%), abdominal pain (0.7%), and anorexia (0.7%).

Treatment-Emergent Adverse Events Among CONCERTA®-Treated Patients: Table 1 enumerates, for a 4-week placebo-controlled, parallel-group trial (Study 3) in children with ADHD at CONCERTA® doses of 18, 36, or 54 mg/day, the incidence of treatment-emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with CONCERTA® where the incidence in patients treated with CONCERTA® was greater than the incidence in placebo-treated patients. 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
Incidence of Treatment-Emergent Events' in a 4-Week Placebo-Controlled Clinical Trial of CONCERTA® in Children

Body System	Preferred Term	CONCERTA® (n=106)	Placebo (n= 99)
General	Headache	14 %	10 %
	Abdominal pain (stomachache)	7 %	1 %
Digestive	Vomiting	4 %	3 %
	Anorexia (loss of appetite)	4 %	0 %
Nervous	Dizziness	2 %	0 %
	Insomnia	4 %	1 %
Respiratory	Upper Respiratory Tract Infection	8 %	5 %
	Cough Increased	4 %	2 %
	Pharyngitis	4 %	3 %
	Sinusitis	3 %	0 %

1: Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 1% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Table 2 lists the incidence of treatment-emergent adverse events for a 2-week placebo-controlled trial (Study 4) in adolescents with ADHD at CONCERTA® doses of 18, 36, 54 or 72 mg/day.

Table 2
Incidence of Treatment-Emergent Events' in a 2-Week Placebo-Controlled Clinical Trial of CONCERTA® in Adolescents

Body System	Preferred Term	CONCERTA® (n=87)	Placebo (n= 90)
General	Accidental injury	6 %	3 %
	Fever	3 %	0 %
	Headache	9 %	8 %
Digestive	Anorexia	2 %	0 %
	Diarrhea	2 %	0 %
	Vomiting	3 %	0 %
Nervous	Insomnia	5 %	0 %
Respiratory	Pharyngitis	2 %	1 %
	Rhinitis	3 %	2 %
Urogenital	Dysmenorrhea	2 %	0 %

1: Events, regardless of causality, for which the incidence for patients treated with CONCERTA® was at least 2% and greater than the incidence among placebo-treated patients. Incidence has been rounded to the nearest whole number.

Tics: In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with CONCERTA®. In a second uncontrolled study (n=682 children) the cumulative incidence of new onset tics was 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

Hypertension: In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® qd and methylphenidate tid increased resting pulse by an average of 2-6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1-4 mm Hg during the day, relative to placebo. In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA® and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA® and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively. (see WARNINGS)

Post-Marketing Experience with CONCERTA®: Post-marketing experiences with CONCERTA® have revealed spontaneous reports of the following adverse events: difficulties in visual accommodation, blurred vision, abnormal liver function test (e.g., transaminase elevation), palpitations, arrhythmia, leucopenia, and thrombocytopenia.

Adverse Events with Other Methylphenidate HCl Products: Nervousness and insomnia are the most common adverse reactions reported with other methylphenidate products. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; headache; dyskinesia; drowsiness; blood pressure and pulse changes, both up and down; tachycardia; angina; abdominal pain; weight loss during prolonged therapy. There have been rare reports of Tourette's syndrome. Toxic psychosis has been reported. Although a definite causal relationship has not been established, the following have been reported in patients taking this drug: hepatic coma; isolated cases of cerebral arteritis and/or occlusion; anemia; transient depressed mood; a few instances of scalp hair loss. Very rare reports of neuroleptic malignant syndrome (NMS) have been received, and, in most of these, patients were concurrently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 18 months experienced an NMS-like event within 45 minutes of ingesting his first dose of venlafaxine. It is uncertain whether this case represented a drug-drug interaction, a response to either drug alone, or some other cause. In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: CONCERTA®, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

Abuse, Dependence, and Tolerance: See WARNINGS for boxed warning containing drug abuse and dependence information.

OVERDOSAGE

Signs and Symptoms: Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis, and dryness of mucous membranes.

Recommended Treatment: Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia. Efficacy of peritoneal dialysis or extracorp real hemodialysis for CONCERTA® overdosage has not been established. The prolonged release of methylphenidate from CONCERTA® should be considered when treating patients with overdose.

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 overdosage with methylphenidate.

Rx Only.

For more information call 1-888-440-7903 or visit www.concerta.net

Manufactured by ALZA Corporation, Mountain View, CA 94043. Distributed and marketed by McNeil Pediatrics, Division of McNeil-PPC, Inc., Fort Washington, PA 19034.

An ALZA OROS® Technology Product

Concerta® and OROS® are Registered Trademarks of ALZA Corporation.

10025003 PI

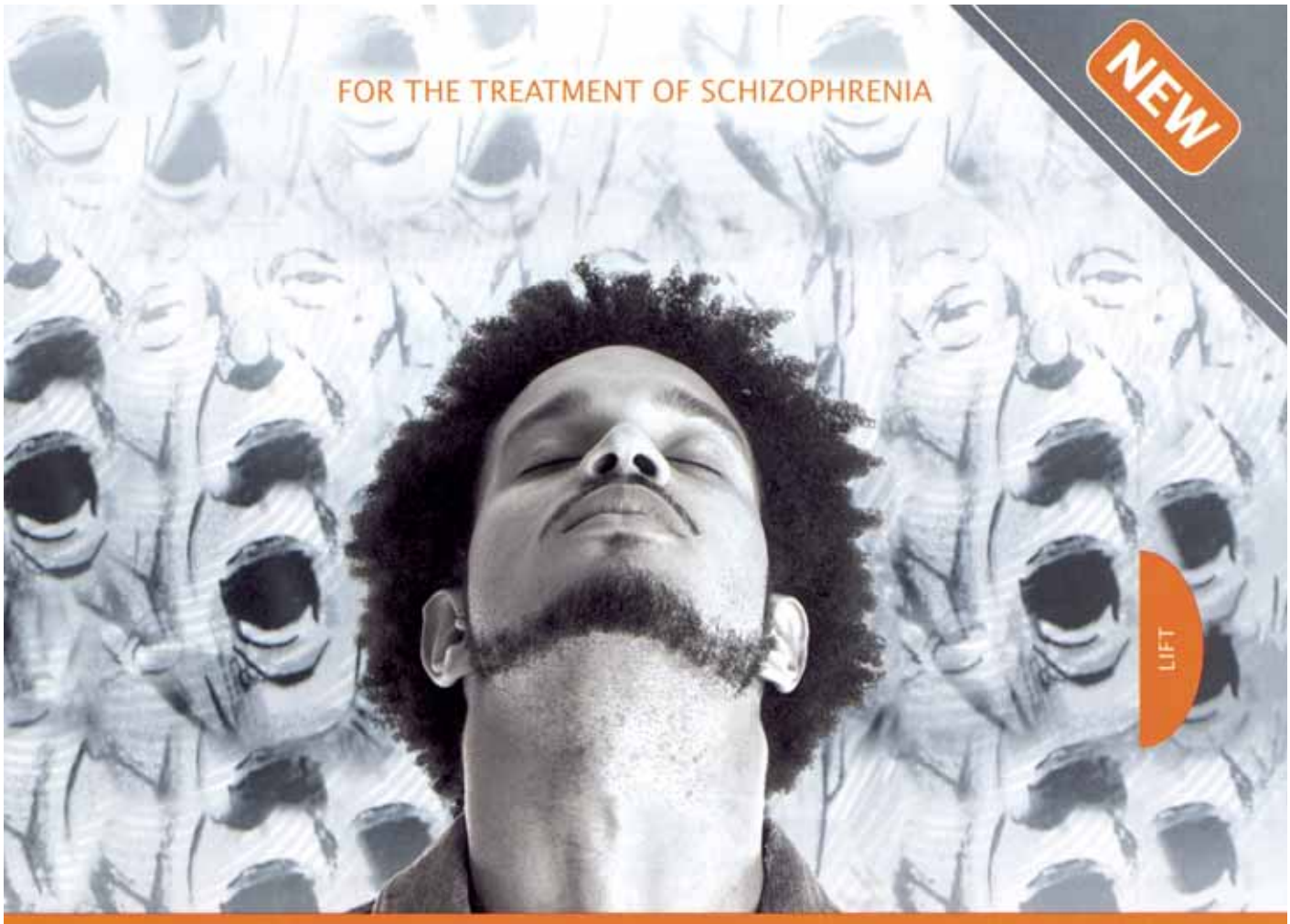
Edition: June 2006

References: **1.** McBurnett K, Cooper KM. Effectiveness of OROS® methylphenidate in children with or without comorbid oppositional defiant disorder and conduct disorder. Poster presented at: American Academy of Child and Adolescent Psychiatry/Canadian Academy of Child and Adolescent Psychiatry Joint Annual Meeting; October 21, 2005; Toronto, Ontario, Canada. **2.** Pelham WE, Gnagy EM, Burrows-Maclean L, et al. Once-a-day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Pediatrics. 2001;107(6). Available at: http://www.pediatrics.org/cgi/content/full/107/6/e105. **3.** Wilens TE, McBurnett K, Bukstein O, et al. Multisite controlled study of OROS methylphenidate in the treatment of adolescents with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med.* 2006;160:82-90.

McNEIL PEDIATRICS
DIVISION OF McNEIL-PPC, INC.

FOR THE TREATMENT OF SCHIZOPHRENIA

NEW



LIFT

He Needs a Powerful Antipsychotic for His Mind

But What Will It Do to His Body?

LIFT

INVEGA™
PALIPERIDONE
Extended-Release Tablets

STRENGTH FOR THE WHOLE PERSON

Please see Important Safety Information, including Boxed Warning, on adjacent pages.
Please see accompanying brief summary of full Prescribing Information for INVEGA™ and RISPERDAL® (risperidone).

A NEW ORAL ATYPICAL ANTIPSYCHOTIC FOR THE TREATMENT OF SCHIZOPHRENIA

INTRODUCING

INVEGA™
PALIPERIDONE
Extended-Release Tablets

STRENGTH FOR THE WHOLE PERSON

IMPORTANT SAFETY INFORMATION FOR INVEGA™ AND RISPERDAL®

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Neither INVEGA™ (paliperidone) nor RISPERDAL® (risperidone) are approved for the treatment of patients with Dementia-Related Psychosis.

INVEGA and RISPERDAL are indicated for the treatment of schizophrenia.

Commonly observed adverse events: The most commonly observed adverse events, occurring at an incidence of ≥5% and at least 2 times placebo, were **INVEGA:** akathisia and extrapyramidal disorder; **RISPERDAL:** anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

QT Prolongation: INVEGA causes a modest increase in the corrected QT (QTc) interval. INVEGA should be avoided in combination with other drugs that are known to prolong the QTc interval, in patients with congenital long QT syndrome or a history of cardiac arrhythmias. Certain circumstances may increase the risk of torsades de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including INVEGA and RISPERDAL. Clinical manifestations include muscle rigidity, fever, altered mental status and evidence of autonomic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Tardive Dyskinesia (TD): TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose. Elderly patients appeared to be at increased risk for TD. Prescribing should be consistent with the need to minimize the risk of TD. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Hyperglycemia and Diabetes: Hyperglycemia, some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics (APS). Patients starting treatment with APS who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

Please see accompanying brief summary of full Prescribing Information for INVEGA and RISPERDAL.

NEW

Powerful Efficacy for the Mind With Safety and Tolerability for the Body

INVEGA combines:

- The active metabolite of RISPERDAL® (risperidone)
- Innovative OROS® extended-release technology

INVEGA demonstrated:

- Significant efficacy in the positive and negative symptoms of schizophrenia[1]
- Low weight gain and EPS rates comparable with placebo in 6-week trials with the recommended 6-mg dose[1]*

Please visit www.invega.com.

Gastrointestinal: INVEGA should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing. Rare instances of obstructive symptoms have been reported in patients with known strictures taking nondeformable formulations. INVEGA should only be used in patients who are able to swallow the tablet whole.

Cerebrovascular Adverse Events (CAEs): CAEs, including fatalities, have been reported in elderly patients with dementia-related psychosis taking atypical antipsychotics in clinical trials. Neither INVEGA nor RISPERDAL are approved for treating these patients.

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

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, INVEGA and RISPERDAL elevate prolactin levels and the elevation persists during chronic administration.

Suicide: The possibility of suicide attempt is inherent in psychotic illnesses and close supervision of high-risk patients should accompany drug therapy.

Orthostatic Hypotension: INVEGA and RISPERDAL may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period. Monitoring should be considered in patients for whom this may be of concern. INVEGA and RISPERDAL should be used with caution in patients with known cardiovascular disease, and conditions that would predispose patients to hypotension.

Potential for Cognitive and Motor Impairment: INVEGA and RISPERDAL have the potential to impair judgment, thinking, or motor skills. Caregivers and patients should use caution until they are reasonably certain that INVEGA and RISPERDAL do not affect them adversely.

Maintenance Treatment: Physicians who elect to use INVEGA and RISPERDAL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Weight Gain: The proportion of subjects having a weight gain of ≥7% body weight were comparable to placebo (5%) for 3 mg (7%) and 6 mg (6%). A higher incidence was seen for 9 mg (9%) and 12 mg (9%).

***Extrapyramidal Symptoms (EPS):** Total EPS-related adverse events in the higher 9-mg and 12-mg treatment groups were 25% and 26%, respectively, versus 11% for the placebo group.

Reference: 1. Data on file. Janssen LP, Titusville, NJ.

Janssen

INVEGA™

(paliperidone)

Extended-Release Tablets

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

Rx only

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these subjects revealed a risk of death in the drug-treated subjects of between 1.6 to 1.7 times that seen in placebo-treated subjects. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated subjects was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. INVEGA™ (paliperidone) Extended-Release Tablets is not approved for the treatment of patients with dementia-related psychosis.

INDICATIONS AND USAGE: INVEGA™ (paliperidone) Extended-Release Tablets is indicated for the treatment of schizophrenia.

CONTRAINDICATIONS: INVEGA™ (paliperidone) is contraindicated in patients with a known hypersensitivity to paliperidone, risperidone, or to any components in the INVEGA™ formulation.

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis – Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. INVEGA™ (paliperidone) Extended-Release Tablets is not approved for the treatment of dementia-related psychosis (see Boxed Warning). QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval. The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia. In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=44) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate-release was more than twice the exposure observed with the maximum recommended 12 mg dose of INVEGA™ ($C_{max\ ss}$ = 113 and 45 ng/mL, respectively, when administered with a standard breakfast). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study. For the three fixed-dose efficacy studies, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the INVEGA™ 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec). No subject receiving INVEGA™ had a QTcLD exceeding 500 msec at any time in any of these three studies. **Neuroleptic Malignant Syndrome:** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Other signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include: discontinuation of the antipsychotic and other drugs not essential to therapy; intensive symptomatic treatment and medical monitoring; and treatment of other serious medical problems. If a patient requires antipsychotic drugs after recovery from NMS, the reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. The risk of developing and likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose. However, tardive dyskinesia can develop, after brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although it may remit, partially or completely, if the antipsychotic is withdrawn. Prescribing should be in a manner to minimize the occurrence. In patients who require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms should appear drug discontinuation should be considered. **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. **Gastrointestinal:** Because the INVEGA™ tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract, INVEGA™ should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet, INVEGA™ should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for Patients). A decrease in transit time, e.g., as seen with diarrhea, would be expected to decrease bioavailability and an increase in transit time, e.g., as seen with gastrointestinal neuropathy, diabetic gastroparesis, or other causes, would be expected to increase bioavailability. These changes in bioavailability are more likely when the changes in transit time occur in the upper GI tract. **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis:** In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. INVEGA™ was not marketed at the time these studies were performed. INVEGA™ is not approved for the treatment of patients with dementia-related psychosis (see also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis).

PRECAUTIONS

General: Orthostatic Hypotension and Syncope: Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA™ (3, 6, 9, 12 mg) compared to 0.3% (1/355) of subjects treated with placebo. INVEGA™ should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension. **Seizures:** Like other antipsychotic drugs, INVEGA™ should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. **Hyperprolactinemia:** Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility). 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, but the available evidence is too limited to be conclusive. **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. INVEGA™ and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy. **Potential for Cognitive and Motor Impairment:** Somnolence and sedation were reported in subjects treated with INVEGA™ (see ADVERSE REACTIONS). Antipsychotics, including INVEGA™, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them. **Priapism:** No cases of priapism have been reported in clinical trials with INVEGA™. **Thrombotic Thrombocytopenia Purpura (TTP):** No cases of TTP were observed during clinical studies with paliperidone. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown. **Body Temperature Regulation:** Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA™ to patients who will be experiencing conditions which may contribute to an elevation in core body temperature. **Antiemetic Effect:** An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor. **Use in Patients with Concomitant Illness:** Clinical experience with INVEGA™ in patients with certain concomitant illnesses is limited (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: Hepatic Impairment and Renal Impairment in full PI). Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome. INVEGA™ has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA™, caution should be observed in patients with known cardiovascular disease (see PRECAUTIONS: General: Orthostatic Hypotension and Syncope). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe INVEGA™. **Orthostatic Hypotension:** Patients should be advised that there is risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose. **Interference With Cognitive and Motor Performance:** As INVEGA™ has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that INVEGA™ therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with INVEGA™. **Nursing:** Patients should be advised not to breast-feed an infant if they are taking INVEGA™. **Concomitant Medication:** Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions. **Alcohol:** Patients should be advised to avoid alcohol while taking INVEGA™. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in avoiding overheating and dehydration. **Administration:** Patients should be informed that INVEGA™ should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice something that looks like a tablet in their stool. **Drug Interactions: Potential for INVEGA™ to Affect Other Drugs** – Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties. At therapeutic concentrations, paliperidone did not inhibit P-glycoprotein. Paliperidone is therefore not expected to inhibit P-glycoprotein-mediated transport of other drugs in a clinically relevant manner. Given the primary CNS effects of paliperidone (see ADVERSE REACTIONS), INVEGA™ should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists. Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA™ is administered with other therapeutic agents that have this potential (see PRECAUTIONS: General: Orthostatic Hypotension and Syncope). **Potential for Other Drugs to Affect INVEGA™** – Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies of paliperidone have not been performed. Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone on a mg/m² basis (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents in terms of human risk is unknown (see PRECAUTIONS: General: Hyperprolactinemia). **Mutagenesis:** No evidence of genotoxic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the *in vivo* rat micronucleus test. **Impairment of Fertility:** In a study of fertility, the percentage of treated female rats that became pregnant was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day. However, pre- and post-implantation loss was increased, and the number of live embryos was slightly decreased, at 2.5 mg/kg, a dose that also caused slight maternal toxicity. These parameters were not affected at a dose of 0.63 mg/kg, which is half of the maximum recommended human dose on a mg/m² basis. The fertility of male rats was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day, although sperm count and sperm viability studies were not conducted with paliperidone. In a subchronic study in Beagle dogs with risperidone, which is extensively converted to paliperidone in dogs and humans, all doses tested (0.31-5.0 mg/kg) resulted in decreases in serum testosterone and in sperm motility and concentration. Serum testosterone and sperm parameters partially recovered, but remained decreased after the last observation (two months after treatment was discontinued). **Pregnancy: Pregnancy Category C:** In studies in rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are 8 times the maximum recommended human dose on a mg/m² basis). In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths were seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m² basis (see risperidone package insert). Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms. There are no adequate and well controlled studies of INVEGA™ in pregnant women. INVEGA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of INVEGA™ on labor and delivery in humans is unknown. **Nursing Mothers:** In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving INVEGA™ should not breast-feed infants. **Pediatric Use:** Safety and effectiveness of INVEGA™ in patients < 18 years of age have not been established. **Geriatric Use:** The safety, tolerability, and efficacy of INVEGA™ were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older). In this study, subjects received flexible doses of INVEGA™ (3 to 12 mg once daily). In addition, a small number of subjects 65 years of age and older were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of INVEGA™ (3 to 15 mg once daily, see CLINICAL PHARMACOLOGY: Clinical Trials in full PI). Overall, of the total number of subjects in clinical studies of INVEGA™ (n = 1796), including those who received INVEGA™ or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with moderate to severe renal impairment (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: Renal Impairment in full PI), who should be given reduced doses. 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: Dosing in Special Populations in full PI).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for INVEGA™ consisting of 2720 patients and/or normal subjects exposed to one or more doses of INVEGA™ for the treatment of schizophrenia. Of these 2720 patients, 2054 were patients who received INVEGA™ while participating in multiple dose, effectiveness trials. The conditions and duration of treatment with INVEGA™ varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose studies, and

short-term and longer-term exposure. Adverse events were assessed by collecting adverse events and performing physical examinations, vital signs, weights, laboratory analyses and ECGs. Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology. The stated frequencies of adverse events represent the proportions of individuals who experienced a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Observed in Short-Term, Placebo-Controlled Trials of Subjects with Schizophrenia** The information presented in these sections were derived from pooled data from the three placebo-controlled, 6-week, fixed-dose studies based on subjects with schizophrenia who received INVEGA™ at daily doses within the recommended range of 3 to 12 mg (n = 850). Adverse Events Occurring at an Incidence of 2% or More Among INVEGA™-Treated Patients with Schizophrenia and More Frequent on Drug than Placebo Table 1 enumerates the pooled incidences of treatment-emergent adverse events that were spontaneously reported in the three placebo-controlled, 6-week, fixed-dose studies, listing those events that occurred in 2% or more of subjects treated with INVEGA™ in any of the dose groups, and for which the incidence in INVEGA™-treated subjects in any of the dose groups was greater than the incidence in subjects treated with placebo. **Treatment-Emergent Adverse Events in Short-Term, Fixed-Dose,Placebo-Controlled Trials in Adult Subjects with Schizophrenia.* Body System or Organ Class** (Dictionary-derived Term) Percentage of Patients Reporting Event INVEGA™ Placebo (N=355) first, INVEGA™ dosage once daily 3 mg (N=127) second, 6 mg N=235) third, 9 mg (N=246) fourth, 12 mg (N=242) fifth, **Total no. subjects with adverse events** 66, 72, 66, 70, 76; **Cardiac disorders:** Atrioventricular block first degree 1, 2, 0, 2, 1; Bundle branch block 2, 3, 1, 3, <1; Sinus arrhythmia 0, 2, 1, 1, <1; Tachycardia 7, 14, 12, 12, 14; **Eye disorders:** Vision blurred 1, 1, <1, 0, 2; **Gastrointestinal disorders:** Abdominal pain upper 1, 1, 3, 2, 2; Dry mouth 1, 2, 3, 1, 3; Dyspepsia 4, 2, 3, 2, 5; Nausea 5, 6, 4, 4, 4; Salivary hypersecretion <1, 0, <1, 1, 4; **General disorders**: Asthenia 1, 2, <1, 2, 2; Fatigue 1, 2, 1, 2, 2; Pyrexia 1, 1, <1, 2, 2; **Investigations:** Blood insulin increased 1, 2, 1, 1, <1; Blood pressure increased 1, 2, <1, <1, 1; Electrocardiogram QT corrected interval prolonged 3, 3, 4, 3, 5; Electrocardiogram T wave abnormal 1, 2, 1, 2, 1; **Musculoskeletal and connective tissue disorders**: Back pain 1, 1, 1, 1, 2; Pain in extremity 1, 0, 1, 0, 2; **Nervous system disorders**: Akathisia 4, 4, 3, 8, 10; Dizziness 4, 6, 5, 4, 5; Dystonia 1, 1, 1, 5, 4; Extrapyramidal disorder 2, 5, 2, 7, 7; Headache 12, 11, 12, 14, 14; Hypertonia 1, 2, 1, 4, 3; Parkinsonism 0, 0, <1, 2, 1; Somnolence 7, 6, 9, 10, 11; Tremor 3, 3, 3, 4, 3; **Psychiatric disorders**: Anxiety 8, 9, 7, 6, 5; **Respiratory, thoracic and mediastinal disorders**: Cough 1, 3, 2, 3, 2; **Vascular disorders**: Orthostatic hypotension 1, 2, 1, 2, 4: *Table includes adverse events that were reported in 2% or more of subjects in any of the INVEGA™ dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from three studies; one included once-daily INVEGA™ doses of 3 and 9 mg, the second study included 6, 9, and 12 mg, and the third study included 6 and 12 mg (see CLINICAL PHARMACOLOGY: Clinical Trials in full PI). Events for which the INVEGA™ incidence was equal to or less than placebo are not listed in the table, but included the following: constipation, diarrhea, vomiting, nasopharyngitis, agitation, and insomnia. **Dose-Related Adverse Events in Clinical Trials:** Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, adverse events that occurred with a greater than 2% incidence in the subjects treated with INVEGA™, the incidences of the following adverse events increased with dose: somnolence, orthostatic hypotension, salivary hypersecretion, akathisia, dystonia, extrapyramidal disorder, hypertonia and Parkinsonism. For most of these, the increased incidence was seen primarily at the 12 mg, and in some cases the 9 mg dose. **Common and Drug-Related Adverse Events in Clinical Trials** Adverse events reported in 5% or more of subjects treated with INVEGA™ and at least twice the placebo rate for at least one dose included: akathisia and extrapyramidal disorder. **Extrapyramidal Symptoms (EPS) in Clinical Trials:** Pooled data from the three placebo-controlled, 6-week, fixed-dose studies provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline) which broadly evaluates Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS, and (4) incidence of spontaneous reports of EPS. For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there was a dose-related increase observed for the 9 mg and 12 mg doses. There was no difference observed between placebo and INVEGA™ 3 mg and 6 mg doses for any of these EPS measures. **Percentage of Patients INVEGA™** Placebo (N=355) first, INVEGA™ dosage once daily 3 mg (N=127) second, 6 mg N=235) third, 9 mg (N=246) fourth, 12 mg (N=242) fifth, **EPS Group:** Parkinsonism [a] 9, 11, 3, 15, 14; Akathisia [b] 6, 6, 4, 7, 9; Use of anticholinergic medications [c] 10, 10, 9, 22, 22: [a]: For Parkinsonism, percent of patients with Simpson-Angus global score > 0.3 (Global score defined as total sum of items score divided by the number of items). [b]: For Akathisia, percent of patients with Barnes Akathisia Rating Scale global score ≥ 2. [c]: Percent of patients who received anticholinergic medications to treat emergent EPS. **Percentage of Patients INVEGA™** Placebo (N=355) first, INVEGA™ dosage once daily 3 mg (N=127) second, 6 mg N=235) third, 9 mg (N=246) fourth, 12 mg (N=242) fifth, **EPS Group**: Overall percentage of patients with EPS-related AE 11.0, 12.6, 10.2, 25.2, 26.0; Dyskinesia 3.4, 4.7, 2.6, 7.7, 8.7; Dystonia 1.1, 0.8, 1.3, 5.3, 4.5; Hyperkinesia 3.9, 3.9, 3.0, 8.1, 9.9; Parkinsonism 2.3, 3.1, 2.6, 7.3, 6.2; Tremor 3.4, 3.1, 2.6, 4.5, 3.3: Dyskinesia group includes: Dyskinesia, Extrapyramidal disorder, Muscle twitching, Tardive dyskinesia Dystonia group includes: Dystonia, Muscle spasms, Oculogyration, Trismus. Hyperkinesia group includes: Akathisia, Hyperkinesia. Parkinsonism group includes: Bradykinesia, Cogwheel rigidity, Drooling, Hypertonia, Hypokinesia, Muscle rigidity, Musculoskeletal stiffness, Parkinsonism. Tremor group includes: Tremor. **Adverse Events Associated with Discontinuation of Treatment in Controlled Clinical Studies:** Overall, there was no difference in the incidence of discontinuation due to adverse events between INVEGA™-treated (5%) and placebo-treated (5%) subjects. The types of adverse events that led to discontinuation were similar for the INVEGA™-and placebo-treated subjects, except for Nervous System Disorders events which were more common among INVEGA™-treated subjects than placebo-treated subjects (2% and 0%, respectively), and Psychiatric Disorders events which were more common among placebo-treated subjects than INVEGA™-treated subjects (3% and 1%, respectively). **Demographic Differences in Adverse Reactions in Clinical Trials:** An examination of population subgroups in the three placebo-controlled, 6-week, fixed-dose studies did not reveal any evidence of differences in safety on the basis of age, gender or race (see PRECAUTIONS: Geriatric Use). **Laboratory Test Abnormalities in Clinical Trials:** In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, between-group comparisons revealed no medically important differences between INVEGA™ and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. Similarly, there were no differences between INVEGA™ and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry. However, INVEGA™ was associated with increases in serum prolactin (see PRECAUTIONS: General: Hyperprolactinemia). **Weight Gain in Clinical Trials:** In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies, the proportions of subjects having a weight gain of ≥ 7% of body weight were similar for INVEGA™ 3 mg and 6 mg (7% and 6%, respectively) and placebo (5%), but there was a higher incidence of weight gain for INVEGA™ 9 mg and 12 mg (9% and 9%, respectively). **Other Events Observed During the Premarketing Evaluation of INVEGA™:** The following list contains all serious and non-serious treatment-emergent adverse events reported at any time by individuals taking INVEGA™ during any phase of a trial within the premarketing database (n = 2720), except (1) those listed in Table 1 above or elsewhere in labeling, (2) those for which a causal relationship to INVEGA™ use was considered remote, and (3) those occurring in only one subject treated with INVEGA™ and that were not acutely life-threatening. Events are classified within body system categories using the following definitions: *very frequent* adverse events are defined as those occurring on one or more occasions in at least 1/10 subjects, *frequent* adverse events are defined as those occurring on one or more occasions in at least 1/100 subjects, *infrequent* adverse events are those occurring on one or more occasions in 1/100 to 1/1000 subjects, and *rare* events are those occurring on one or more occasions in less than 1/1000 subjects. **Blood and Lymphatic System Disorders:** *rare:* thrombocytopenia; **Cardiac Disorders:** *frequent:* palpitations; *infrequent*: bradycardia; **Gastrointestinal Disorders:** *frequent:* abdominal pain; *infrequent*: swollen tongue; **General Disorders:** *infrequent:* edema; **Immune Disorder:** *rare*: anaphylactic reaction; **Nervous System Disorders:** *rare*: coordination abnormal; **Psychiatric Disorders:** *infrequent*: confusional state; **Respiratory, Thoracic and Mediastinal Disorders:** *frequent*: dyspnea; *rare*: pulmonary embolus; **Vascular Disorders:** *rare*: ischemia, venous thrombosis; **Adverse Events Reported With Risperidone**; Paliperidone is the major active metabolite of risperidone. Adverse events reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone package insert.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: INVEGA™ (paliperidone) is not a controlled substance.

For more information on symptoms and treatment of overdosage, see full Prescribing Information.

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RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

RISPERDAL® M-TAB®
(RISPERIDONE)
ORALLY DISINTEGRATING TABLETS

Brief Summary of Full Prescribing Information for Schizophrenia and Bipolar Mania. CLINICAL STUDIES FOR OTHER INDICATIONS WILL HAVE DIFFERING ADVERSE EVENTS AND SAFETY CONCERNS. PLEASE SEE FULL PI FOR THIS INFORMATION REGARDING RISPERDAL® FOR AUTISM.

Increased Mortality in Elderly Patients with Dementia–Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

INDICATIONS AND USAGE: RISPERDAL® (risperidone) is indicated for the treatment of schizophrenia. **Monotherapy:** RISPERDAL® is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder. **Combination Therapy:** The combination of RISPERDAL® with lithium or valproate is indicated for the short-term treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

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

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. RISPERDAL® (risperidone) is not approved for the treatment of dementia-related psychosis (see Boxed Warning). Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Other signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include: discontinuation of the antipsychotic and other drugs not essential to therapy; intensive symptomatic treatment and medical monitoring; and treatment of other serious medical problems. If a patient requires antipsychotic drugs after recovery from NMS, the reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. The risk of developing and likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose. However, tardive dyskinesia can develop, after brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although it may remit, partially or completely, if the antipsychotic is withdrawn. Prescribing should be in a manner to minimize the occurrence. In patients who require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms should appear drug discontinuation should be considered. **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis:** Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients (mean age 85 years; range 73-97) in trials of risperidone in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with risperidone compared to patients treated with placebo. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Hyperglycemia and Diabetes Mellitus:** Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including RISPERDAL®. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.

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 and 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 in full PI). 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. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Hyperprolactinemia:** As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). 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 patients with schizophrenia and bipolar mania, including children and adolescent patients, 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. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, are reported to have an increased sensitivity to antipsychotic medications. Manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. 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 discuss the following issues with patients for whom they prescribe RISPERDAL®: **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. **Interference With Cognitive and Motor Performance:** Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Nursing:** Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®. **Concomitant Medication:** Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. **Alcohol:** Patients should be advised to avoid alcohol while taking RISPERDAL®. **Phenylketonurics:** Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg phenylalanine; each 2 mg RISPERDAL® M-TAB®

Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine. **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. Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. **Carbamazepine and Other Enzyme Inducers:** In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9–hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9–hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. **Fluoxetine and Paroxetine:** Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9–hydroxyrisperidone. Paroxetine lowered the concentration of 9–hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9–hydroxyrisperidone have not been studied. **Lithium:** Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13). **Valproate:** Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone. **Digoxin:** RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin. **Drugs That Inhibit CYP 2D6 and Other CYP Isozymes:** Risperidone is metabolized to 9–hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY in full PI). 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 CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism. There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY in full PI). **Drugs Metabolized by CYP 2D6:** *In vitro* studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6. **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 recommended human dose (MRHD) for schizophrenia (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. These findings are considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General - Hyperprolactinemia). **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 (MRHD) on a mg/m^2 basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 basis. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. 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:** In animal studies, risperidone and 9–hydroxyrisperidone are excreted in milk. Risperidone and 9–hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed. **Pediatric Use:** The safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or bipolar mania have not been established. **Tardive Dyskinesia:** In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, 2 (0.1%) patients were reported to have tardive dyskinesia, which resolved on discontinuation of risperidone treatment (see WARNINGS – Tardive Dyskinesia). **Weight Gain:** In long-term, open-label trials (studies in patients with autistic disorder or other psychiatric disorders), a mean increase of 7.5 kg after 12 months of RISPERDAL® treatment was observed, which was higher than the expected normal weight gain (approximately 3 to 3.5 kg per year adjusted for age, based on Centers for Disease Control and Prevention normative data). The majority of that increase occurred within the first 6 months of exposure to RISPERDAL®. The average percentiles at baseline and 12 months, respectively, were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index. When treating patients with RISPERDAL®, weight gain should be assessed against that expected with normal growth. (See also ADVERSE REACTIONS.) **Somnolence:** Somnolence was frequently observed in placebo-controlled clinical trials of pediatric patients with autistic disorder. Most cases were mild or moderate in severity. These events were most often of early onset with peak incidence occurring during the first two weeks of treatment, and transient with a median duration of 16 days. (See also ADVERSE REACTIONS.) Patients experiencing persistent somnolence may benefit from a change in dosing regimen. **Hyperprolactinemia, Growth, and Sexual Maturation:** Risperidone has been shown to elevate prolactin levels in children and adolescents as well as in adults (see PRECAUTIONS - Hyperprolactinemia). In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years), 49% of patients who received risperidone had elevated prolactin levels compared to 2% of patients who received placebo. In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, galactorrhea was reported in 0.8% of risperidone-treated patients and gynecomastia was reported in 2.3% of risperidone-treated patients. The long-term effects of risperidone on growth and sexual maturation have not been fully evaluated. **Geriatric Use:** Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than 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 in full PI). 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 substantially excreted by the kidneys, 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 in full PI). **Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis:** In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**.)

ADVERSE REACTIONS: Associated With Discontinuation of Treatment: Bipolar Mania: In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%). In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo). **Incidence in Controlled Trials: Commonly Observed Adverse Events in Controlled Clinical Trials:** ***Bipolar Mania:*** In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence. *Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania:* Adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms. *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial-Monotherapy in Bipolar Mania.* **Body System/Preferred Term: Central & peripheral nervous system:** Dystonia, Akathisia, Dizziness, Parkinsonism, Hypoaesthesia **Psychiatric:** Somnolence, Agitation, Manic reaction, Anxiety, Concentration impaired **Gastrointestinal system:** Dyspepsia, Nausea, Saliva increased, Mouth dry **Body as a whole - general:** Pain, Fatigue, Injury **Respiratory system:** Sinusitis, Rhinitis, Coughing **Skin and appendages:** Acne, Pruritus **Musculo-Skeletal:** Myalgia, Skeletal pain **Metabolic and nutritional:** Weight increase **Vision disorders:** Vision abnormal **Cardiovascular, general:** Hypertension, Hypotension **Heart rate and rhythm:** Tachycardia. *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial – Adjunctive Therapy in Bipolar Mania.* **Body System/Preferred Term: Gastrointestinal system:** Saliva increased, Diarrhea, Abdominal pain, Constipation, Mouth dry, Tooth ache, Tooth disorder **Central & peripheral nervous system:** Dizziness, Parkinsonism, Akathisia, Dystonia **Psychiatric:** Somnolence, Anxiety, Confusion **Respiratory system:** Rhinitis, Pharyngitis, Coughing **Body as a whole - general:** Asthenia **Urinary system:** Urinary incontinence **Heart rate and rhythm:** Tachycardia **Metabolic and nutritional:** Weight increase **Skin and appendages:** Rash. **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 fatigability, 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:*** Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). **Adverse Events and Other Safety Measures in Pediatric Patients With Autistic Disorder:** In the two 8-week, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder (n=156), two patients (one treated with RISPERDAL® and one treated with placebo) discontinued treatment due to an adverse event. *Incidence of Treatment-Emergent Adverse Events in Two 8-Week, Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder.* **Body System Preferred Term: Psychiatric:** Somnolence, Appetite increased, Confusion **Gastrointestinal:** Saliva increased, Constipation, Dry mouth **Body as a whole - general:** Fatigue **Central & peripheral nervous system:** Tremor, Dystonia, Dizziness, Automatism, Dyskinesia, Parkinsonism **Respiratory**: Upper respiratory tract infection **Metabolic and nutritional**: Weight increase **Heart rate and rhythm**: Tachycardia **Other Events Observed During the Premarketing Evaluation of RISPERDAL®:** During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 adult patients with schizophrenia and 1923 pediatric 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. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it). Serious adverse reactions experienced by the pediatric population were similar to those seen in the adult population (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS). **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. **Gastrointestinal 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:** *Infrequent:* granulocytopenia. *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, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pituitary adenomas, pulmonary embolism, precocious puberty, and QT prolongation. 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 more information on symptoms and treatment of overdosage, see full Prescribing Information.

7503233SB Revised December 2006

Janssen L.P

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PSYCHIATRY
BOARD REVIEW SERIES
THE KAUFMAN COURSES

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This intensive three-day weekend course, offered for the 35th year, is designed for psychiatrists in practice and in residency as an update or board preparation. Focusing on essential topics, the course will use lectures, extensive syllabus, and the new edition of Clinical Neurology for Psychiatrists, David M. Kaufman (6th edition, Elsevier).

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Friday, September 7 to Sunday, September 9, 2007
7:45 AM – 5:00 PM

NEW YORK
The Graduate Center, Concourse Level
City University of New York (CUNY)
Friday, October 5 to Sunday, October 7, 2007
8:15 AM – 5:15 PM

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Andrea J. Weiss, MD and David Myland Kaufman, MD

This two-day course will be a pre-test that will complement standard psychiatry review courses and complete the review in Clinical Neurology for Psychiatrists. In this course, an expert group of faculty who are experienced and well-informed about modern psychiatry and test-taking strategies will present essential information through a series of test-type questions utilizing audience response system keypads and using answers for discussions and explanations.

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Monday, September 10 to Tuesday, September 11, 2007
7:45 AM – 5:00 PM

NEW YORK
The Graduate Center, Concourse Level
City University of New York (CUNY)
Monday, October 8 to Tuesday, October 9, 2007
8:15 AM – 5:15 PM

MAINTENANCE OF CERTIFICATION (THE RECERT COURSE)
Dan Smuckler, MD, Andrea J. Weiss, MD and David Myland Kaufman, MD

This intensive two-day course designed for psychiatrists will review the psychiatric information likely to appear on the recertification examination. It will cover current evidence-based treatments for psychiatric disorders, emphasizing clinical matters and advances in diagnosis and treatment. Presentation of the material will be in a mixed format, with both lecture and question and answer utilizing audience response system keypads.

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The Graduate Center, Main Level
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8:15 AM – 5:15 PM

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MASTER THE FINE ART OF SLEEP

PRESCRIBE LUNESTA FIRST-LINE—FOR A FULL 7 TO 8 HOURS OF SLEEP

LUNESTA has been studied in large, well-controlled clinical trials in **all** of the following patient types:

- ✔ Patients With Insomnia Comorbid With Major Depressive Disorder
- ✔ Patients With Insomnia Comorbid With Generalized Anxiety Disorder
- ✔ Patients With Insomnia Comorbid With Rheumatoid Arthritis
- ✔ Patients With Insomnia Comorbid With Menopause

The failure of insomnia to remit after 7 to 10 days of treatment should be medically evaluated.

LUNESTA is indicated for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, LUNESTA administered at bedtime decreased sleep latency and improved sleep maintenance. LUNESTA is not indicated for the treatment of depression, generalized anxiety disorder, rheumatoid arthritis, or menopause.

Important Safety Information

LUNESTA, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, LUNESTA 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 should not take LUNESTA unless they are prepared to get a full night's sleep. As with other hypnotics, patients receiving LUNESTA 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 LUNESTA. In clinical trials, the most common adverse events associated with LUNESTA were unpleasant taste, headache, somnolence, dizziness, dry mouth, infection, and pain.

Any night or every night

Leave the rest to...

Lunesta®
(eszopiclone)C
1, 2 AND 3 MG TABLETS

LUNESTA has been classified as a Schedule IV controlled substance. Sedative hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. These patients should be under careful surveillance when receiving LUNESTA or any other hypnotic. Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

LUNESTA, like 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. LUNESTA should not be taken with alcohol. Dosage adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents because of the potentially additive effects.

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. See dosage and administration in complete prescribing information.

Please see brief summary of complete prescribing information.

Lunesta®
(eszopiclone)©
1, 2 AND 3 MG TABLETS

BRIEF SUMMARY

INDICATIONS AND USAGE
LUNESTA is indicated for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, LUNESTA administered at bedtime decreased sleep latency and improved sleep maintenance.

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 LUNESTA. Because some of the important adverse effects of LUNESTA appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly (see **DOSAGE AND ADMINISTRATION in the Full Prescribing Information**).

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 (e.g., 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**).

LUNESTA, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, LUNESTA 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 LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (e.g., operating machinery or driving a motor vehicle) after ingesting the drug, and be cautioned about potential impairment of the performance of such activities on the day following ingestion of LUNESTA. LUNESTA, like 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. LUNESTA should not be taken with alcohol. Dose adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents, because of the potentially additive effects.

PRECAUTIONS
General
Timing Of Drug Administration: LUNESTA should be taken immediately before bedtime. Taking a sedative/hypnotic 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. The recommended starting dose of LUNESTA for these patients is 1 mg (see **DOSAGE AND ADMINISTRATION in the Full Prescribing Information**).

Use In Patients With Concomitant Illness: Clinical experience with eszopiclone in patients with concomitant illness is limited. Eszopiclone should be used with caution in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

A study in healthy volunteers did not reveal respiratory-depressant effects at doses 2.5-fold higher (7 mg) than the recommended dose of eszopiclone. Caution is advised, however, if LUNESTA is prescribed to patients with compromised respiratory function.

The dose of LUNESTA should be reduced to 1 mg in patients with severe hepatic impairment, because systemic exposure is doubled in such subjects. No dose adjustment appears necessary for subjects with mild or moderate hepatic impairment. No dose adjustment appears necessary in subjects with any degree of renal impairment, since less than 10% of eszopiclone is excreted unchanged in the urine.

The dose of LUNESTA should be reduced in patients who are administered potent inhibitors of CYP3A4, such as ketoconazole, while taking LUNESTA. Downward dose adjustment is also recommended when LUNESTA is administered with agents having known CNS-depressant effects.

Use In Patients With Depression: Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; 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: An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol 0.70 g/kg for up to 4 hours after ethanol administration.

Paroxetine: Coadministration of single doses of eszopiclone 3 mg and paroxetine 20 mg daily for 7 days produced no pharmacokinetic or pharmacodynamic interaction.

Lorazepam: Coadministration of single doses of eszopiclone 3 mg and lorazepam 2 mg did not have clinically relevant effects on the pharmacodynamics or pharmacokinetics of either drug.

Olanzapine: Coadministration of eszopiclone 3 mg and olanzapine 10 mg produced a decrease in DSST scores. The interaction was pharmacodynamic; there was no alteration in the pharmacokinetics of either drug.

Drugs That Inhibit CYP3A4 (Ketoconazole): CYP3A4 is a major metabolic pathway for elimination of eszopiclone. The AUC of eszopiclone was increased 2.2-fold by coadministration of ketoconazole, a potent inhibitor of CYP3A4, 400 mg daily for 5 days. C_{max} and $t_{1/2}$ were increased 1.4-fold and 1.3-fold, respectively. Other strong inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, nefazodone, troleandomycin, ritonavir, nelfinavir) would be expected to behave similarly.

Drugs That Induce CYP3A4 (Rifampicin): Racemic zopiclone exposure was decreased 80% by concomitant use of rifampicin, a potent inducer of CYP3A4. A similar effect would be expected with eszopiclone.

Drugs Highly Bound To Plasma Protein: Eszopiclone is not highly bound to plasma proteins (52-59% bound); therefore, the disposition of eszopiclone is not expected to be sensitive to alterations in protein binding. Administration of eszopiclone 3 mg to a patient taking another drug that is highly protein-bound would not be expected to cause an alteration in the free concentration of either drug.

Drugs With A Narrow Therapeutic Index

Digoxin: A single dose of eszopiclone 3 mg did not affect the pharmacokinetics of digoxin measured at steady state following dosing of 0.5 mg twice daily for one day and 0.25 mg daily for the next 6 days.

Warfarin: Eszopiclone 3 mg administered daily for 5 days did not affect the pharmacokinetics of (R)- or (S)-warfarin, nor were there any changes in the pharmacodynamic profile (prothrombin time) following a single 25-mg oral dose of warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: In a carcinogenicity study in Sprague-Dawley rats in which eszopiclone was given by oral gavage, no increases in tumors were seen; plasma levels (AUC) of eszopiclone at the highest dose used in this study (16 mg/kg/day) are estimated to be 80 (females) and 20 (males) times those in humans receiving the maximum recommended human dose (MRHD). However, in a carcinogenicity study in Sprague-Dawley rats in which racemic zopiclone was given in the diet, and in which plasma levels of eszopiclone were reached that were greater than those reached in the above study of eszopiclone, an increase in mammary gland adenocarcinomas in females and an increase in thyroid gland follicular cell adenomas and carcinomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 150 (females) and 70 (males) times those in humans receiving the MRHD. The mechanism for the increase in mammary adenocarcinomas is unknown. The increase in thyroid tumors is thought to be due to increased levels of TSH secondary to increased metabolism of circulating thyroid hormones, a mechanism that is not considered to be relevant to humans.

In a carcinogenicity study in B6C3F1 mice in which racemic zopiclone was given in the diet, an increase in pulmonary carcinomas and carcinomas plus adenomas in females and an increase in skin fibromas and sarcomas in males were seen at the highest dose of 100 mg/kg/day. Plasma levels of eszopiclone at this dose are estimated to be 8 (females) and 20 (males) times those in humans receiving the MRHD. The skin tumors were due to skin lesions induced by aggressive behavior, a mechanism that is not relevant to humans. A carcinogenicity study was also performed in which CD-1 mice were given eszopiclone at doses up to 100 mg/kg/day by oral gavage; although this study did not reach a maximum tolerated dose, and was thus inadequate for overall assessment of carcinogenic potential, no increases in either pulmonary or skin tumors were seen at doses producing plasma levels of eszopiclone estimated to be 90 times those in humans receiving the MRHD—i.e., 12 times the exposure in the racemate study.

Eszopiclone did not increase tumors in a p53 transgenic mouse bioassay at oral doses up to 300 mg/kg/day.

Mutagenesis: Eszopiclone was positive in the mouse lymphoma chromosomal aberration assay and produced an equivocal response in the Chinese hamster ovary cell chromosomal aberration assay. It was not mutagenic or clastogenic in the bacterial Ames gene mutation assay, in an unscheduled DNA synthesis assay, or in an *in vivo* mouse bone marrow micronucleus assay.

(S)-N-desmethyl zopiclone, a metabolite of eszopiclone, was positive in the Chinese hamster ovary cell and human lymphocyte chromosomal aberration assays. It was negative in the bacterial Ames mutation assay, in an *in vitro* ^{32}P-postlabeling DNA adduct assay, and in an *in vivo* mouse bone marrow chromosomal aberration and micronucleus assay.

Impairment Of Fertility: Eszopiclone was given by oral gavage to male rats at doses up to 45 mg/kg/day from 4 weeks premating through mating and to female rats at doses up to 180 mg/kg/day from 2 weeks premating through day 7 of pregnancy. An additional study was performed in which only females were treated, up to 180 mg/kg/day. Eszopiclone decreased fertility, probably because of effects in both males and females, with no females becoming pregnant when both males and females were treated with the highest dose; the no-effect dose in both sexes was 5 mg/kg (16 times the MRHD on a mg/m^2 basis). Other effects included increased preimplantation loss (no-effect dose 25 mg/kg), abnormal estrus cycles (no-effect dose 25 mg/kg), and decreases in sperm number and motility and increases in morphologically abnormal sperm (no-effect dose 5 mg/kg).

Pregnancy
Pregnancy Category C: Eszopiclone administered by oral gavage to pregnant rats and rabbits during the period of organogenesis showed no evidence of teratogenicity up to the highest doses tested (250 and 16 mg/kg/day in rats and rabbits, respectively; these doses are 800 and 100 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). In the rat, slight reductions in fetal weight and evidence of developmental delay were seen at maternally toxic doses of 125 and 150 mg/kg/day, but not at 62.5 mg/kg/day (200 times the MRHD on a mg/m^2 basis). Eszopiclone was also administered by oral gavage to pregnant rats throughout the pregnancy and lactation periods at doses of up to 180 mg/kg/day. Increased postimplantation loss, decreased postnatal pup weights and survival, and increased pup startle response were seen at all doses; the lowest dose tested, 60 mg/kg/day, is 200 times the MRHD on a mg/m^2 basis. These doses did not produce significant maternal toxicity. Eszopiclone had no effects on other behavioral measures or reproductive function in the offspring.

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

Labor And Delivery: LUNESTA has no established use in labor and delivery.

Nursing Mothers: It is not known whether LUNESTA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LUNESTA is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of eszopiclone in children below the age of 18 have not been established.

Geriatric Use: A total of 287 subjects in double-blind, parallel-group, placebo-controlled clinical trials who received eszopiclone were 65 to 86 years of age. The overall pattern of adverse events for elderly subjects (median age = 71 years) in 2-week studies with nighttime dosing of 2 mg eszopiclone was not different from that seen in younger adults. LUNESTA 2 mg exhibited significant reduction in sleep latency and improvement in sleep maintenance in the elderly population.

ADVERSE REACTIONS
The premarketing development program for LUNESTA included eszopiclone exposures in patients and/or normal subjects from two different groups of studies: approximately 400 normal subjects in clinical pharmacology/pharmacokinetic studies, and approximately 1550 patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 263 patient-exposure years. The conditions and duration of treatment with LUNESTA varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term and longer-term exposure. 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 tabulations 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. An event was considered treatment-emergent if it occurred for the first time or worsened while the patient was receiving therapy following baseline evaluation.

Adverse Findings Observed in Placebo-Controlled Trials
Adverse Events Resulting in Discontinuation of Treatment: In placebo-controlled, parallel-group clinical trials in the elderly, 3.8% of 208 patients who received placebo, 2.3% of 215 patients who received 2 mg LUNESTA, and 1.4% of 72 patients who received 1 mg LUNESTA discontinued treatment due to an adverse event. In the 6-week parallel-group study in adults, no patients in the 3 mg arm discontinued because of an adverse event. In the long-term 6-month study in adult insomnia patients, 7.2% of 195 patients who received placebo and 12.8% of 593 patients who received 3 mg LUNESTA discontinued due to an adverse event. No event that resulted in discontinuation occurred at a rate of greater than 2%.

Adverse Events Observed at an Incidence of ≥2% in Controlled Trials. The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from a Phase 3 placebo-controlled study of LUNESTA at doses of 2 or 3 mg in non-elderly adults. Treatment duration in this trial was 44 days. Data are limited to adverse events that occurred in 2% or more of patients treated with LUNESTA 2 mg (n=104) or 3 mg (n=105) in which the incidence in patients treated with LUNESTA was greater than the incidence in placebo-treated patients (n=99).[1]

Body as a whole: headache (13%, 21%, 17%), viral infection (1%, 3%, 3%). Digestive system: dry mouth (3%, 5%, 7%), dyspepsia (4%, 4%, 5%), nausea (4%, 5%, 4%), vomiting (1%, 3%, 0%). Nervous system: anxiety (0%, 3%, 1%), confusion (0%, 0%, 3%), depression (0%, 4%, 1%), dizziness (4%, 5%, 7%), hallucinations (0%, 1%, 3%), libido decreased (0%, 0%, 3%), nervousness (3%, 5%, 0%), somnolence (3%, 10%, 8%). Respiratory system: infection (3%, 5%, 10%). Skin and appendages: rash (1%, 3%, 4%). Special senses: unpleasant taste (3%, 17%, 34%). Urogenital system: dysmenorrhea* (0%, 3%, 0%), gynecomastia** (0%, 3%, 0%).

*Gender-specific adverse event in females

**Gender-specific adverse event in males

[1]Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abdominal dreams, accidental injury, back pain, diarrhea, flu syndrome, myalgia, pain, pharyngitis, and rhinitis.

Adverse events that suggest a dose-response relationship in adults include viral infection, dry mouth, dizziness, hallucinations, infection, rash, and unpleasant taste, with this relationship clearest for unpleasant taste.

The following lists the incidence (% placebo, 2 mg, 3 mg, respectively) of treatment-emergent adverse events from combined Phase 3 placebo-controlled studies of LUNESTA at doses of 1 or 2 mg in elderly adults (ages 65-86). Treatment duration in these trials was 14 days. Data are limited to events that occurred in 2% or more of patients treated with LUNESTA 1 mg (n=72) or 2 mg (n=215) in which the incidence in patients treated with LUNESTA was greater than the incidence in placebo-treated patients.[1]

Body as a whole: accidental injury (1%, 0%, 3%), headache (14%, 15%, 13%), pain (2%, 4%, 5%). Digestive system: diarrhea (2%, 4%, 2%), dry mouth (2%, 3%, 7%), dyspepsia (2%, 6%, 2%). Nervous system: abnormal dreams (0%, 3%, 1%), dizziness (2%, 1%, 6%), nervousness (1%, 0%, 2%), neuralgia (0%, 3%, 0%). Skin and appendages: pruritus: (1%, 4%, 1%). Special senses: unpleasant taste (0%, 8%, 12%). Urogenital system: urinary tract infection (0%, 3%, 0%).

[1]Events for which the LUNESTA incidence was equal to or less than placebo are not listed, but included the following: abdominal pain, asthenia, nausea, rash, and somnolence.

Adverse events that suggest a dose-response relationship in elderly adults include pain, dry mouth, and unpleasant taste, with this relationship again clearest for unpleasant taste. These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice because patient characteristics and other factors may differ from those that 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 contributions of drug and non-drug factors to the adverse event incidence rate in the population studied.

Other Events Observed During The Premarketing Evaluation Of LUNESTA. Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section and reported by approximately 1550 subjects treated with LUNESTA at doses in the range of 1 to 3.5 mg/day during Phase 2 and 3 clinical trials throughout the United States and Canada. All reported events are included except those already listed here or listed elsewhere in labeling, minor events common in the general population, and events unlikely to be drug-related. Although the events reported occurred during treatment with LUNESTA, they were not necessarily caused by it.

Events are listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those that occurred on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those that occurred in fewer than 1/100 patients but in at least 1/1,000 patients; **rare** adverse events are those that occurred in fewer than 1/1,000 patients. Gender-specific events are categorized based on their incidence for the appropriate gender.

Frequent: chest pain, migraine, peripheral edema.

Infrequent: acne, agitation, allergic reaction, alopecia, amenorrhea, anemia, anorexia, apathy, arthritis, asthma, ataxia, breast engorgement, breast enlargement, breast neoplasm, breast pain, bronchitis, bursitis, cellulitis, cholelithiasis, conjunctivitis, contact dermatitis, cystitis, dry eyes, dry skin, dyspnea, dysuria, eczema, ear pain, emotional lability, epistaxis, face edema, female lactation, fever, halitosis, heat stroke, hematuria, hernia, hiccup, hostility, hypercholesteremia, hypertension, hypertonia, hypesthesia, incoordination, increased appetite, insomnia, joint disorder (mainly swelling, stiffness, and pain), kidney calculus, kidney pain, laryngitis, leg cramps, lymphadenopathy, malaise, mastitis, melena, memory impairment, menorrhagia, metrorrhagia, mouth ulceration, myasthenia, neck rigidity, neurosis, nystagmus, otitis externa, otitis media, paresthesia, photosensitivity, reflexes decreased, skin discoloration, sweating, thinking abnormal (mainly difficulty concentrating), thirst, tinnitus, twitching, ulcerative stomatitis, urinary frequency, urinary incontinence, urticaria, uterine hemorrhage, vaginal hemorrhage, vaginitis, vertigo, vestibular disorder, weight gain, weight loss.

Rare: abnormal gait, arthrosis, colitis, dehydration, dysphagia, erythema multiforme, euphoria, furunculosis, gastritis, gout, hepatitis, hepatomegaly, herpes zoster, hirsutism, hyperacusis, hyperesthesia, hyperlipemia, hypokalemia, hypokinesia, iritis, liver damage, maculopapular rash, mydriasis, myopathy, neuritis, neuropathy, oliguria, photophobia, ptosis, pyelonephritis, rectal hemorrhage, stomach ulcer, stomatitis, stupor, thrombophlebitis, tongue edema, tremor, urethritis, vesiculobullous rash.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: LUNESTA is a Schedule IV controlled substance under the Controlled Substances Act. Other substances under the same classification are benzodiazepines and the nonbenzodiazepine hypnotics zaleplon and zolpidem. While eszopiclone is a hypnotic agent with a chemical structure unrelated to benzodiazepines, it shares some of the pharmacologic properties of the benzodiazepines.

Abuse, Dependence, and Tolerance
Abuse and Dependence: In a study of abuse liability conducted in individuals with known histories of benzodiazepine abuse, eszopiclone at doses of 6 and 12 mg produced euphoric effects similar to those of diazepam 20 mg. In this study, at doses 2-fold or greater than the maximum recommended doses, a dose-related increase in reports of amnesia and hallucinations was observed for both LUNESTA and diazepam.

The clinical trial experience with LUNESTA revealed no evidence of a serious withdrawal syndrome. Nevertheless, the following adverse events included in DSM-IV criteria for uncomplicated sedative/hypnotic withdrawal were reported during clinical trials following placebo substitution occurring within 48 hours following the last LUNESTA treatment: anxiety, abnormal dreams, nausea, and upset stomach. These reported adverse events occurred at an incidence of 2% or less. Use of benzodiazepines and similar agents may lead to physical and psychological dependence. The risk of abuse and dependence increases with the dose and duration of treatment and concomitant use of other psychoactive drugs. The risk is also greater for patients who have a history of alcohol or drug abuse or history of psychiatric disorders. These patients should be under careful surveillance when receiving LUNESTA or any other hypnotic.

Tolerance: Some loss of efficacy to the hypnotic effect of benzodiazepines and benzodiazepine-like agents may develop after repeated use of these drugs for a few weeks.

No development of tolerance to any parameter of sleep measurement was observed over six months. Tolerance to the efficacy of LUNESTA 3 mg was assessed by 4-week objective and 6-week subjective measurements of time to sleep onset and sleep maintenance for LUNESTA in a placebo-controlled 44-day study, and by subjective assessments of time to sleep onset and WASO in a placebo-controlled study for 6 months.

OVERDOSAGE
There is limited premarketing clinical experience with the effects of an overdosage of LUNESTA. In clinical trials with eszopiclone, one case of overdose with up to 36 mg of eszopiclone was reported in which the subject fully recovered. Individuals have fully recovered from racemic zopiclone overdoses up to 340 mg (56 times the maximum recommended dose of eszopiclone).

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. Impairment of consciousness ranging from somnolence to coma has been described. Rare individual instances of fatal outcomes following overdose with racemic zopiclone have been reported in European postmarketing reports, most often associated with overdose with other CNS-depressant agents.

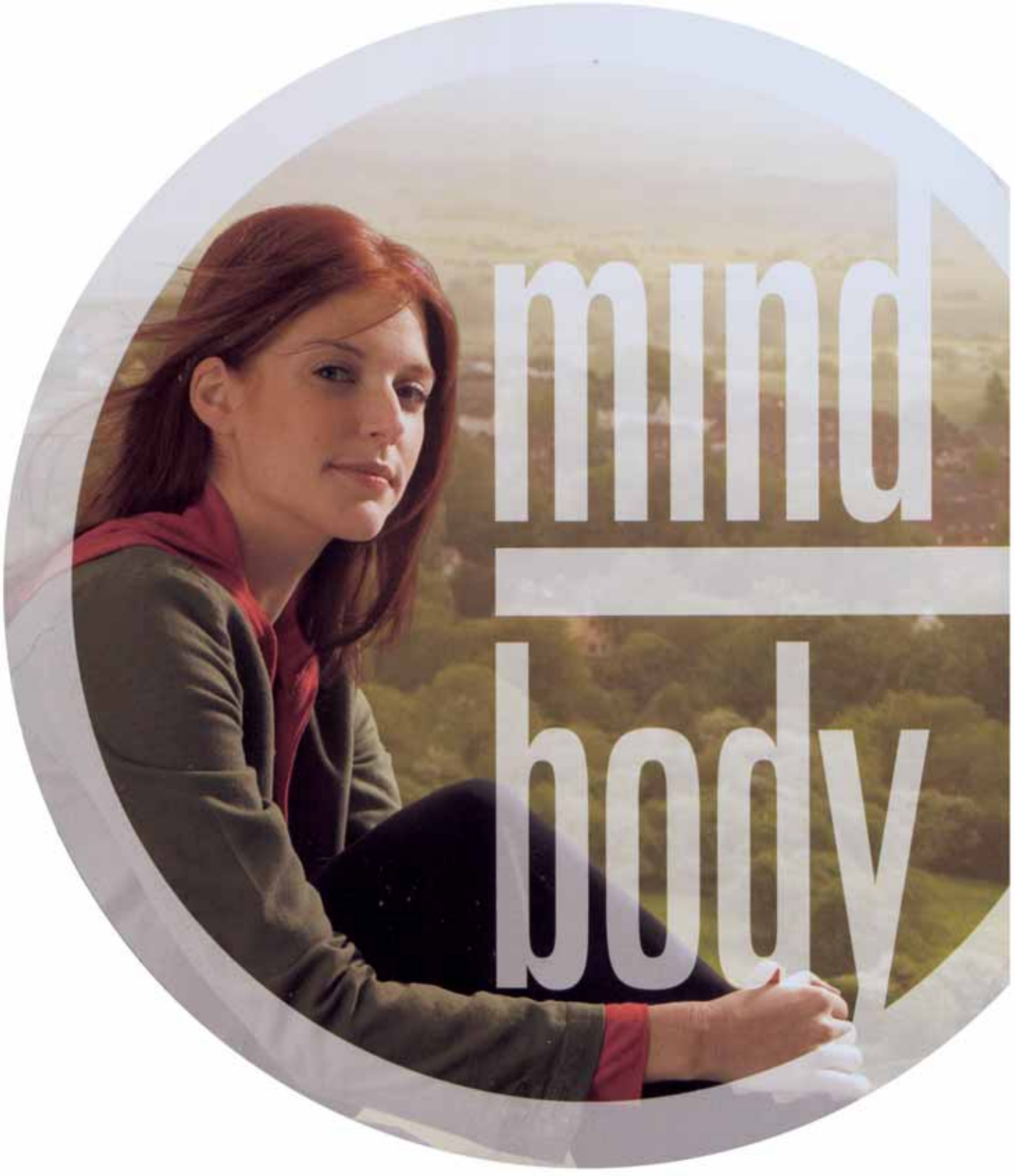
Recommended Treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical intervention. The value of dialysis in the treatment of overdosage has not been determined.

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.

Rx only.

SEPRACOR 12/06


OPEN
Because she does not like to compromise…

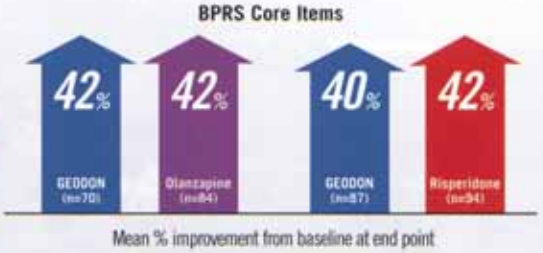

mind
body

IN SCHIZOPHRENIA

Treat With the Body in Mind

CHOOSE COMPARABLE POWER...

Consistent results in acute head-to-head studies[1-3]



A 6-week, double-blind, randomized study of GEODON vs olanzapine and an 8-week, double-blind, randomized study of GEODON vs risperidone.

- BPRS core items include hallucinatory behavior, unusual thought content, conceptual disorganization, and suspiciousness
- Comparable efficacy was maintained in double-blind extension studies
  —up to 1 year vs risperidone[1]
  —up to 6 months vs olanzapine[4]

...WITHOUT COMPROMISING METABOLIC PARAMETERS

Significant results in switch studies after 1 year[1,3]

Two 1-year open-label extensions of 6-week, open-label switch studies in patients suboptimally controlled due to partial response or poor tolerability.

- Patients switching to GEODON from olanzapine and risperidone also experienced reductions in triglycerides[3]

In the acute head-to-head studies...

- In the GEODON vs olanzapine study, olanzapine significantly increased body weight (8 lb vs 2 lb for GEODON, $P<0.0001$)[1,2]
- In the GEODON vs risperidone study, risperidone increased body weight (2 lb vs 0 lb for GEODON, $P<0.01$)[1,3]

GEODON is indicated for the treatment of schizophrenia.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT_c interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first.

Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

In short-term schizophrenia trials, 10% of GEODON-treated patients experienced a weight gain of ≥7% of body weight vs 4% for placebo. In the same short-term trials, the most common adverse events were somnolence (14%) and respiratory tract infection (8%).

Pfizer

CHOOSE GEODON®
(ziprasidone HCl) **Oral Capsules**

Please see brief summary of prescribing information, including boxed warning, on adjacent page.

BRIEF SUMMARY. See package insert for full prescribing information.

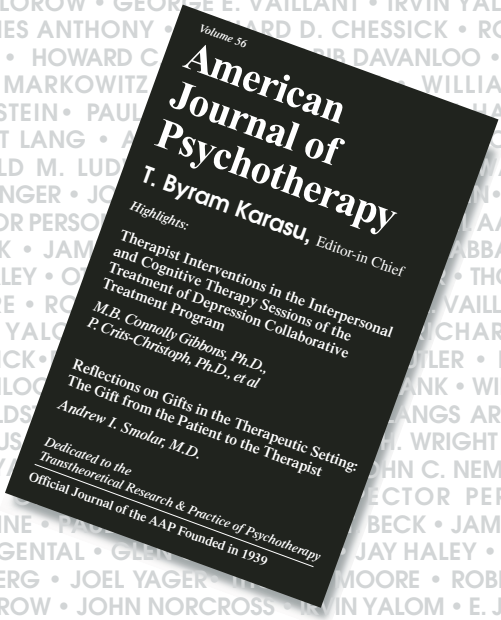
Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. GEODON (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

INDICATIONS—GEODON Capsules is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. GEODON® (ziprasidone mesylate) for Injection is indicated for acute agitation in schizophrenic patients.

CONTRAINDICATIONS — *QT Prolongation:* Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS—Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning). *QT Prolongation and Risk of Sudden Death:* GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT_c prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec. *Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. 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 (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS — *General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis).** Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. 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 in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole*, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum zprolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m² basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m² basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m² basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS — *Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** 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. Schizophrenia: Body as a Whole—*Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System—*Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System—*Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine—*Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System—*Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders—*Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hyperproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System—*Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System—*Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System—*Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages—*Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses—*Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System—*Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE—*Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/95).

References: 1. Data on file. Pfizer Inc, New York, NY. **2.** Simpson GM, Glick ID, Weiden PJ, Romano SJ, Siu CO. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry.* 2004;161:1837-1847. **3.** Addington DEN, Pantelis C, Dineen M, Benattia I, Romano SJ. Efficacy and tolerability of ziprasidone versus risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder: an 8-week, double-blind, multicenter trial. *J Clin Psychiatry.* 2004;65:1624-1633. **4.** Simpson GM, Weiden P, Pigott T, Murray S, Siu CO, Romano SJ. Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia. *Am J Psychiatry.* 2005;162:1535-1538. **5.** Weiden PJ, Loebel A, Yang R, Lebovitz H. Course of weight & metabolic benefits 1 year after switching to ziprasidone. Presented at: American Psychiatric Association Annual Meeting; May 1-6, 2004; New York, NY.

Revised November 2006



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APA 2007 ANNUAL MEETING SPONSORED BY THE AMERICAN PSYCHIATRIC ASSOCIATION

NAVIGATING THE COMPLEX MAZE OF BIPOLAR DISORDER

Monday, May 21, 2007

6:30 – 7:00 PM Dinner
7:00 – 10:00 PM Symposium

Manchester Grand Hyatt San Diego
Douglas Pavillion C/D
One Market Place
San Diego, California

EDUCATIONAL OBJECTIVES

At the end of this educational activity participants should be able to

1) List major obstacles to the diagnosis of bipolar disorder and describe strategies for distinguishing bipolar disorder from depression and agitated depression.
2) Describe common psychiatric and medical comorbidities in bipolar patients, and their implications for treatment.
3) Outline major findings from STEP-BD and their implications for clinical practice

ACCREDITATION

The American Psychiatric Association (APA) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The APA designates this educational activity of a maxiumum of *3 AMA PRA category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activty.

Attendees must be registered for the 2007 APA Annual Meeting to attend this symposium. Seating is limited and will be on a first-come, first-served basis. For more information about the meeting, please visit the APA web site at www.psych.org or contact the APA toll free at 1-888-357-7924 (within the US or Canada) or 703-907-7300.

Registered conference participants and registered guests may attend an industry-supported symposium at the APA meeting.

Sponsored by the American Psychiatric Association.

Supported by an educational grant from Pfizer, Inc.

AGENDA

7:00–7:10 PM
Opening Remarks
Prakash Masand, MD–Chairman
Duke University Medical Center

7:10–7:40 PM
Diagnostic Pitfalls in Patients with Bipolar Disorder
Prakash Masand, MD

7:40–8:10 PM
Managing the Bipolar Patient with Medical Comorbidities
Andrea Fagiolini, MD
University of Pittsburgh School of Medicine

8:10–8:40 PM
Tailoring Antipsychotic Treatment to the Complex Patient with Bipolar Disorder
Paul E. Keck, Jr., MD
University of Cincinnati College of Medicine

8:40–9:10 PM
Bringing Research to the Clinician: Lessons from STEP-BD
Gary Sachs, MD
Massachusetts General Hospital

9:10–9:55 PM
Panel Discussion
Faculty Panel

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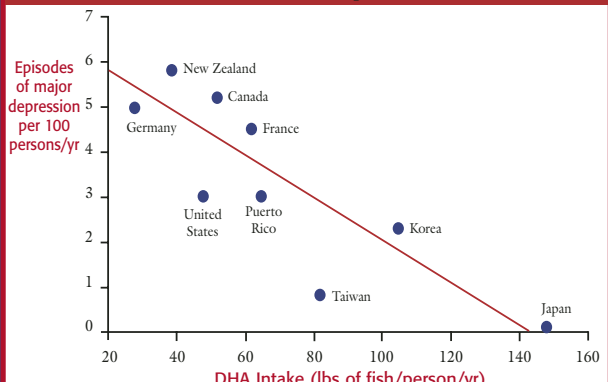
Alcohol Consumption	✔	✔

DHA Intake Predicts Prevalence of Depression



Adapted from Hibbeln, J.R. *Lancet* 1998;351:1213.

"There is good evidence that psychiatric illness is associated with depletion of [Omega-3] and, crucially, that supplementation can result in clinical amelioration."
Hallahan, B., & Garland, M.R. *British J Psych* 2005;186:275-277.

Postpartum–"...lower DHA content in mothers' milk...[was] associated with higher rates of postpartum depression."
Hibbeln, J.R. *J Affect Disord* 2002;69:15-29.

"Trials have shown that folate supplementation hastens recovery from depressive episodes and enhances the effect of antidepressants."
Morris, M.S., et al. *Psychother and Psychosom* 2003;72(2):80-7.

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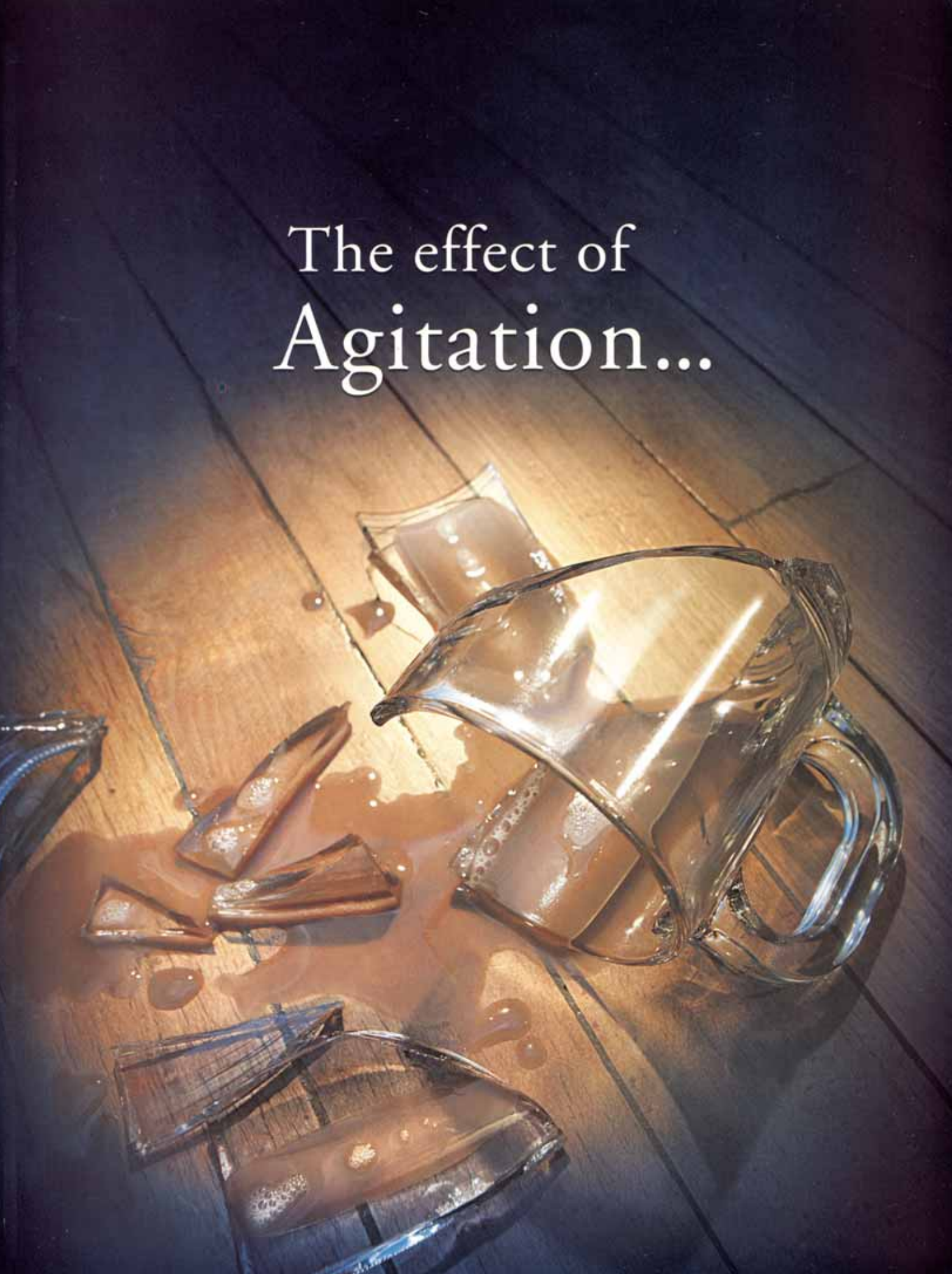
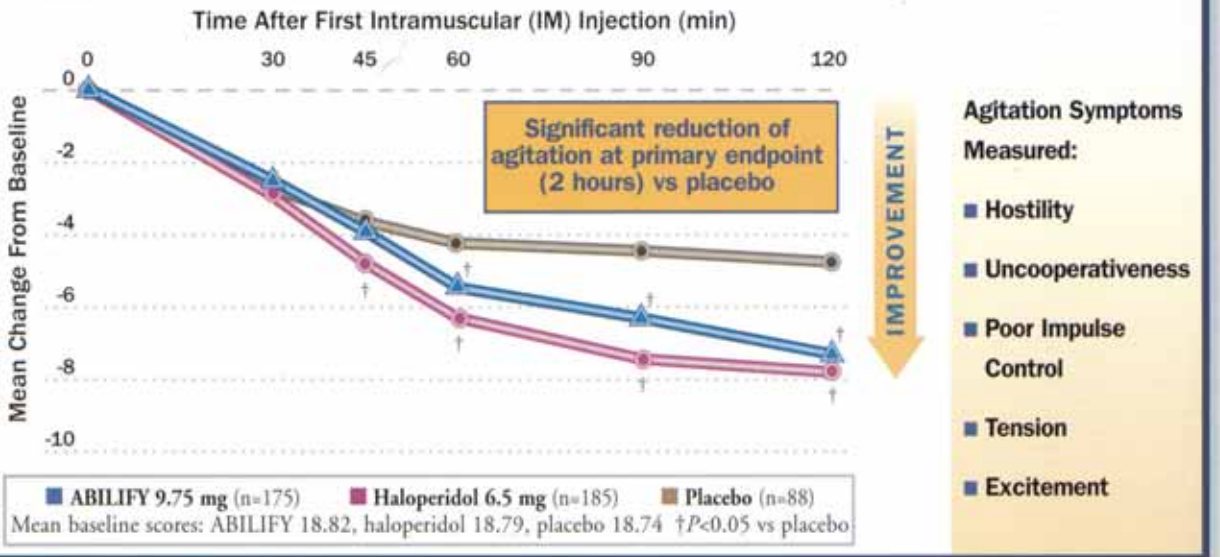

The effect of
Agitation...


The effect of a start toward long-term symptom control
A
Physicians who elect to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

In schizophrenia or bipolar mania

ABILIFY® (aripiprazole) Injection Rapidly Controls Agitation[1]

Significant reduction in symptoms of agitation in schizophrenia as measured by PANSS™-EC score*



Adapted from Andrezina et al. *Psychopharmacology (Berl).* 2006.

*Last observation carried forward.

See study description on next page.

PANSS™-EC=Positive and Negative Syndrome Scale Excited Component.

PANSS™ is a trademark of Multi-Health Systems, Inc.

ABILIFY Injection is indicated for the treatment of agitation associated with schizophrenia or bipolar mania

ABILIFY is also indicated for the treatment of schizophrenia including maintaining stability in patients who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer and observed for relapse during a period of up to 26 weeks.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Please see IMPORTANT SAFETY INFORMATION, including **Boxed WARNING**, on next page.

ABILIFY® (aripiprazole)
INJECTION 9.75 mg/1.3 mL

HELP ILLUMINATE THE PERSON WITHIN

IMPORTANT SAFETY INFORMATION for ABILIFY® (aripiprazole)

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). ABILIFY is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).

- **Neuroleptic malignant syndrome (NMS)**–As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation is recommended
- **Tardive dyskinesia (TD)**–The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, discontinuation should be considered since TD may remit, partially or completely
- **Cerebrovascular adverse events** (eg, stroke, transient ischemic attack), including fatalities, have been reported at an increased incidence in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY
- **Hyperglycemia and diabetes mellitus**–Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ABILIFY. Patients with diabetes should be monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. There have been few reports of hyperglycemia with ABILIFY

Treatment-emergent adverse events reported with:

ABILIFY Oral

In short-term trials of patients with schizophrenia (up to 6 weeks) or bipolar disorder (up to 3 weeks), the following were reported at an incidence ≥10% and greater than placebo, respectively: headache (30% vs 25%), anxiety (20% vs 17%), insomnia (19% vs 14%), nausea (16% vs 12%), vomiting (12% vs 6%), dizziness (11% vs 8%), constipation (11% vs 7%), dyspepsia (10% vs 8%), and akathisia (10% vs 4%).

ABILIFY Injection

In short-term (24 hour) trials, the following were reported at an incidence ≥5% and greater than placebo, respectively: headache (12% vs 7%), nausea (9% vs 3%), dizziness (8% vs 5%), and somnolence (7% vs 4%).

ABILIFY®(aripiprazole) offers your patients:

- Rapid control of agitation*[1]
- Early and sustained symptom control
- Low potential of unwanted sedation
- Favorable weight and lipid profile
  - In a 52-week schizophrenia trial, the percentage of patients with ≥7% increase in baseline body weight was 30% for those with BMI <23, 19% for those with BMI 23 to 27, and 8% for those with BMI >27.

*With ABILIFY Injection at primary endpoint (2 hours).

Physicians who elect to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Study Description:

Double-blind, placebo-controlled, randomized, multicenter study conducted with 448 patients. If needed, concomitant benzodiazepine (lorazepam [4 mg/day] or equivalent) could be administered at least 60 minutes after the second injection. After completing the 24-hour IM phase, patients received blinded oral tablet study medication corresponding to their initial treatment arm for 4 days. Patients randomized to aripiprazole or placebo during the 24-hour IM phase received 15-mg aripiprazole oral tablets (with the option of decreasing to 10-mg aripiprazole based on clinical judgment).

Reference:

1. Andreatini R, Josiassen RC, Marcus RN, et al. Intramuscular aripiprazole for the treatment of acute schizophrenia or schizoaffective disorder: a double-blind, placebo-controlled comparison with intramuscular haloperidol. *Psychopharmacology (Berl)*. 2006;188:281-292.

Please see accompanying Brief Summary of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, for ABILIFY on following pages.

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Rx only

BRIEF SUMMARY: PLEASE CONSULT PACKAGE INSERT FOR COMPLETE PRESCRIBING INFORMATION.

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

CONTRAINDICATIONS: Known hypersensitivity to aripiprazole

WARNINGS: Increased Mortality In Elderly Patients With Dementia-Related Psychosis - Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).

Neuroleptic Malignant Syndrome (NMS): Potentially fatal NMS has been reported in association with administration of antipsychotic drugs, including ABILIFY. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If signs and symptoms appear, immediate discontinuation is recommended (see **Full Prescribing Information for additional information on management of NMS**). Patients requiring antipsychotic drug treatment after recovery from NMS should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia (TD): Potentially irreversible TD may develop in patients treated with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are more likely to develop the syndrome. The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, discontinuation should be considered since TD may remit, partially or completely. Antipsychotic treatment, itself, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. The need for continued treatment should be reassessed periodically.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis: In placebo-controlled clinical studies (two flexible-dose and one fixed-dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients. In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. ABILIFY is not approved for the treatment of patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS** and **PRECAUTIONS** in **Full Prescribing Information**.)

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including ABILIFY. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Patients diagnosed with diabetes who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control; patients with risk factors for diabetes should undergo baseline and periodic fasting blood glucose (FBG) testing. Any patient being treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia and those who develop symptoms of hyperglycemia should also undergo FBG testing.

PRECAUTIONS: General:

Orthostatic Hypotension: ABILIFY may be associated with orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on oral ABILIFY included: orthostatic hypotension (1.9%), postural dizziness (0.8%), and syncope (0.6%). The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on oral ABILIFY included: orthostatic hypotension (0.7%), postural dizziness (0.5%), and syncope (0.3%). The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials in agitation associated with schizophrenia or bipolar mania (n=501) on ABILIFY Injection included: orthostatic hypotension (0.6%), postural dizziness (0.2%), and syncope (0.4%). The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo in trials in patients with schizophrenia, bipolar mania, or agitation associated with schizophrenia or bipolar mania. ABILIFY should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). If parenteral benzodiazepine therapy is deemed necessary in addition to ABILIFY Injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension.

Seizures: In short-term trials, seizures/convulsions occurred in 0.1% (1/926) of oral aripiprazole-treated patients with schizophrenia, in 0.3% (2/597) of oral aripiprazole-treated patients with bipolar mania, and in 0.2% (1/501) of aripiprazole injection-treated patients with agitation associated with schizophrenia or bipolar mania. Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment: Despite the relatively modest increased incidence of somnolence compared to placebo, ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. In short-term trials, somnolence (including sedation) was reported in 10% of patients with schizophrenia on oral ABILIFY compared to 8% of patients on placebo; 14% of patients with bipolar mania on oral ABILIFY compared to 7% of patients on placebo; and in 9% of patients with agitation associated with schizophrenia or bipolar mania on ABILIFY Injection compared to 6% of patients on placebo. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Use appropriate care when prescribing aripiprazole for patients who will be experiencing conditions that may contribute to an elevation in core body temperature.

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

Suicide: The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY should be written for the smallest quantity consistent with good patient management.

Use in Patients with Concomitant Illness: Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses is limited. ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease.

In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938), the treatment-emergent adverse events that were reported at an incidence of ≥3% and aripiprazole incidence at least twice that for placebo were lethargy, somnolence (including sedation), incontinence (primarily, urinary incontinence), excessive salivation, and lightheadedness. ABILIFY is not approved for treatment of patients with dementia-related psychosis. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration (See **Boxed WARNING, WARNINGS** and **CLINICAL PHARMACOLOGY: Special Populations** in **Full Prescribing Information**.)

Information for Patients: Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY (aripiprazole). See Full Prescribing Information for the complete information to discuss with patients taking ABILIFY:

Interference with Cognitive and Motor Performance: Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ABILIFY does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY.

Nursing: Patients should be advised not to breast-feed an infant if they are taking ABILIFY.

Concomitant Medication: Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Phenylketonurics: Phenylalanine is a component of aspartame. Each ABILIFY DISCMELT orally disintegrating tablet contains the following amounts: 10 mg - 1.12 mg phenylalanine and 15 mg - 1.68 mg phenylalanine.

Sugar Content: Patients should be advised that each mL of ABILIFY oral solution contains 400 mg of sucrose and 200 mg of fructose.

Drug Interactions: Use caution when ABILIFY is taken in combination with other centrally acting drugs and alcohol. ABILIFY may enhance the effect of certain antihypertensive agents. ABILIFY is unlikely to cause clinically important drug interactions mediated by the enzymes CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. *In vivo* studies using 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole.

Inducers of CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. When a **CYP3A4** inducer is added to ABILIFY, the dose of ABILIFY should be doubled. Additional dose increases should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from combination therapy, the ABILIFY dose should be reduced.

Carbamazepine: Coadministration of carbamazepine (200 mg BID) with ABILIFY (30 mg QD) resulted in an approximate 70% decrease in C_{max} and AUC values of aripiprazole and its active metabolite, dehydro-aripiprazole.

Inhibitors of CYP3A4 (eg, ketoconazole) or **CYP2D6** (eg, quinidine, fluoxetine, or paroxetine) can inhibit the elimination of aripiprazole and cause increased blood levels. When a strong **CYP3A4** or **CYP2D6** inhibitor is added to ABILIFY, the dose of ABILIFY should be reduced to one-half of the usual dose. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, the ABILIFY dose should then be increased.

Ketoconazole: Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of ABILIFY increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively.

Quinidine: Coadministration of a 10-mg single dose of ABILIFY with quinidine (166 mg/day for 13 days) increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%.

Alcohol: There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and at 10, 20, 40, 60 mg/kg/day (3 to 19 times the maximum recommended human dose [MRHD] based on mg/m^2) to SD rats and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the MRHD based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years. Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2). These findings are considered to be prolactin-mediated. Increases in serum prolactin were observed in a 13-week dietary study in female mice at doses used in the carcinogenicity study. Serum prolactin was not increased in a 4- and 13-week dietary study in female rats. The relevance for human risk of prolactin-mediated endocrine tumors in rodents is unknown. **Mutagenesis:** Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the *in vivo* micronucleus assay in mice; however, the response was shown to be due to a mechanism not considered relevant to humans. **Impairment of Fertility:** Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the MRHD on an mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg. Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on an mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Aripiprazole should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Labor and Delivery: The effect of aripiprazole on labor and delivery in humans is unknown.

Nursing Mothers: Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

Pediatric Use: Safety and effectiveness in pediatric and adolescent patients have not been established.

Geriatric Use: Placebo-controlled studies of oral aripiprazole in schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects (≥65 years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients. Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. (See also **Boxed WARNING, WARNINGS** and **PRECAUTIONS** in **Full Prescribing Information**.)

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 8456 patients who participated in multiple-dose, clinical trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5635 patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole injection. A total of 2442 patients were treated with oral aripiprazole for at least 180 days and 1667 patients treated with oral aripiprazole had at least 1 year of exposure.

Adverse Events Associated with Discontinuation of Treatment: Overall, there was little difference in the incidence of discontinuation due to adverse events in placebo-controlled oral aripiprazole trials (aripiprazole vs placebo: schizophrenia, 7% vs 9%; bipolar mania, 11% vs 9%; or in placebo-controlled intramuscular aripiprazole injection trials (aripiprazole injection, 0.8%; placebo 0.5%). The types of adverse events that led to discontinuation were similar between the oral aripiprazole and placebo-treated patients.

Commonly Observed Adverse Events: (≥5% incidence and at a rate at least twice the rate of placebo for ABILIFY vs placebo, respectively): In 4- to 6-week, placebo-controlled, schizophrenia trials (2 to 30 mg/day), the one commonly observed adverse event associated with the use of oral aripiprazole was: akathisia (8%, 4%). In 3-week, placebo-controlled, bipolar mania trials (15 or 30 mg/day), the most common adverse events associated with oral aripiprazole were: akathisia (15%, 3%), constipation (13%, 6%), sedation (8%, 3%), tremor (7%, 3%), restlessness (6%, 3%), extrapyramidal disorder (5%, 2%). In 24-hour placebo-controlled trials of intramuscular aripiprazole injection for agitation associated with schizophrenia or bipolar mania, nausea was the one adverse event observed (9%, 3%).

Adverse Events with an Incidence ≥2% in Oral Aripiprazole Trials: The following treatment-emergent

events were reported at an incidence of ≥2% with oral aripiprazole (doses ≥2 mg/d), and at a greater incidence with aripiprazole than with placebo in short-term placebo-controlled trials (aripiprazole N=1523, placebo N=849), respectively, were: headache (30%, 25%), anxiety (20%, 17%), insomnia (19%, 14%), nausea (16%, 12%), vomiting (12%, 6%), dizziness (11%, 8%), constipation (11%, 7%), dyspepsia (10%, 8%), akathisia (10%, 4%), sedation (7%, 4%), fatigue (6%, 5%), extrapyramidal disorder (6%, 4%), somnolence (5%, 4%), dry mouth (5%, 4%), arthralgia (5%, 4%), tremor (5%, 3%), restlessness (5%, 3%), pharyngolaryngeal pain (4%, 3%), pain in extremity (4%, 2%), cough (3%, 2%), nasal congestion (3%, 2%), abdominal discomfort (3%, 2%), stomach discomfort (3%, 2%), pain (3%, 2%), vision blurred (3%, 1%), salivary hypersecretion (2%, 1%), peripheral edema (2%, 1%), hypertension (including blood pressure increased) (2%, 1%). The following events were reported by patients treated with oral aripiprazole with an incidence equal to or less than placebo: diarrhea, toothache, upper abdominal pain, abdominal pain, musculoskeletal stiffness, back pain, myalgia, agitation, psychotic disorder, dysmenorrhea (percentage based on gender total), and rash.

Adverse Events with an Incidence ≥1% in Intramuscular Aripiprazole Injection Trials: The following treatment-emergent events were reported at an incidence ≥1% with intramuscular aripiprazole injection (doses ≥5.25 mg/day) and at incidence greater than placebo in 24-hour, placebo-controlled trials (aripiprazole injection N=501, placebo N=220) in agitated patients with schizophrenia or bipolar mania, respectively, include: headache (12%, 7%), nausea (9%, 3%), dizziness (8%, 5%), somnolence (7%, 4%), sedation (3%, 2%), vomiting (3%, 1%), fatigue (2%, 1%), tachycardia (2%, <1%), akathisia (2%, 0%), dyspepsia (1%, <1%), dry mouth (1%, <1%), blood pressure increased (1%, <1%), musculoskeletal stiffness (1%, <1%). The following events were reported by patients treated with aripiprazole injection with an incidence equal to or less than placebo: injection site pain, injection site burning, insomnia, agitation.

Dose-Related Adverse Events: Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in patients with schizophrenia comparing various fixed doses (2, 5, 10, 15, 20, and 30 mg/day) of oral aripiprazole to placebo. The one adverse event to have a possible dose response relationship was somnolence (including sedation) which was most prominent at the 30 mg/day dose (placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

Extrapyramidal Symptoms: In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS-related events, excluding events related to akathisia was (oral aripiprazole 13%, placebo 12%) and the incidence of akathisia-related events was (oral aripiprazole 8%, placebo 4%). In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events, excluding events related to akathisia was (oral aripiprazole 15%, placebo 8%) and the incidence of akathisia-related events was (oral aripiprazole 15%, placebo 4%). In the placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia was (aripiprazole injection 2%, placebo 2%) and the incidence of akathisia-related events was (aripiprazole injection 2%, placebo 0%).

Laboratory Test Abnormalities: A between group comparison for 3- to 6-week, placebo-controlled trials revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. In a long-term (26-week), placebo-controlled trial there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, and total cholesterol measurements.

Weight Gain: In 4- to 6-week trials in schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively), and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)]. In 3-week trials in mania, the mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. -0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (3%) compared to placebo (2%). In a 26-week schizophrenia trial, weight change, respectively, for ABILIFY (aripiprazole)- and placebo-treated patients was -0.5 kg and -0.5 kg for those with BMI <23, -1.3 kg and -0.6 kg for those with BMI 23 to 27, and -2.1 kg and -1.5 kg for those with BMI >27. The percentage of ABILIFY- and placebo-treated patients, respectively, with ≥7% increase in baseline body weight was 6.8% and 3.7% for those with BMI <23, 5.1% and 4.2% for those with BMI 23 to 27, and 5.7% and 4.1% for those with BMI >27. In a 52-week schizophrenia trial, weight change for ABILIFY-treated patients was 2.6 kg for those with BMI <23, 1.4 kg for those with BMI 23 to 27, and -1.2 kg for those with BMI >27. The percentage of ABILIFY-treated patients with ≥7% increase in baseline body weight was 30% for those with BMI <23, 19% for those with BMI 23 to 27, and 8% for those with BMI >27.

ECG Changes: Pooled analysis of placebo-controlled trials in patients with schizophrenia or bipolar mania treated with oral aripiprazole or in patients with agitation associated with schizophrenia or bipolar mania treated with intramuscular aripiprazole injection, revealed no significant differences between aripiprazole and placebo of potentially important changes in ECG parameters. Oral aripiprazole was associated with a median increase in heart rate of 5 beats per minute compared to a 1 beat per minute increase among placebo patients.

Adverse Events in Long-Term, Double-Blind, Placebo-Controlled Trials

The adverse events reported in a 26-week, double-blind trial comparing oral ABILIFY and placebo in patients with schizophrenia or bipolar mania were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor (ABILIFY 8% vs placebo 2%).

Other Adverse Events Observed During the Premarketing Evaluation of Oral Aripiprazole

The following adverse events were reported with oral aripiprazole at multiple doses ≥2 mg/day in clinical trials (8456 patients, 5365 patient-years of exposure). This list may not include events previously listed elsewhere in the labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening. *Frequent events* are those occurring in at least 1/100 patients; *infrequent events* are those occurring in 1/100 to 1/1000 patients; *rare events* are those occurring in fewer than 1/1000 patients. ***Blood and Lymphatic System Disorders:*** *Infrequent* - anaemia, lymphadenopathy, leukopenia (including agranulocytosis, neutropenia); *Rare* - leukocytosis, thrombocytopenia, idiopathic thrombocytopenic purpura, thrombocythaemia. ***Cardiac Disorders:*** *Frequent* - tachycardia (including ventricular, supraventricular, sinus); *Infrequent* - bradycardia, palpitations, cardiac failure (including congestive and acute), myocardial infarction, cardiac arrest, atrial fibrillation, atrioventricular block (including first degree and complete), extrasystoles (including ventricular and supraventricular), angina pectoris, cyanosis, bundle branch block (including left, right), myocardial ischaemia; *Rare* - atrial flutter, cardiomegaly, cardiomyopathy, cardiopulmonary failure. ***Ear and Labyrinth Disorders:*** *Infrequent* - ear pain, vertigo, tinnitus; *Rare* - deafness. ***Endocrine Disorders:*** *Infrequent* - hypothyroidism; *Rare* - goitre, hyperparathyroidism, hyperthyroidism. ***Eye Disorders:*** *Frequent* - conjunctivitis; *Infrequent* - eye redness, eye irritation, dry eye, blepharospasm, visual disturbance, eye pain, eye discharge, blepharitis, cataract, lacrimation increased; *Rare* - eyelid function disorder, oculogyration, eyelid oedema, photophobia, diplopia, eyelid ptosis, eye haemorrhage. ***Gastrointestinal Disorders:*** *Frequent* - loose stools; *Infrequent* - flatulence, dysphagia, gastroesophageal reflux disease, gastritis, haemorrhoids, abdominal distension, faecal incontinence, haematochezia, gingival pain, rectal haemorrhage, abdominal pain lower, oral pain, retching, faecaloma, gastrointestinal haemorrhage, ulcer (including gastric, duodenal, peptic), tooth fracture, gingivitis, lip dry; *Rare* - abdominal tenderness, chapped lips, periodontitis, aptyalism, gastrointestinal pain, hypoaesthesia oral, inguinal hernia, swollen tongue, colitis, haematemesis, hyperchlorhydria, irritable bowel syndrome, oesophagitis, faeces hard, gingival bleeding, glossodynia, mouth ulceration, reflux oesophagitis, cheilitis, intestinal obstruction, pancreatitis, eructation, gastric ulcer haemorrhage, melaena, glossitis, stomatitis. ***General Disorders and Administration Site Conditions:*** *Frequent* - asthenia, pyrexia, chest pain, gait disturbance; *Infrequent* - malaise, oedema, influenza-like illness, chills, general physical health deterioration, feeling jittery, mobility decreased, thirst, feeling cold, difficulty in walking, facial pain, sluggishness, condition aggravated; *Rare* - inflammation localized, swelling, energy increased, inflammation, abasia, xerosis, feeling hot, hyperthermia, hypothermia. ***Hepatobiliary Disorders:*** *Infrequent* - cholecystitis (including acute and chronic); *Rare* - cholelithiasis, hepatitis. ***Immune System Disorders:*** *Infrequent* - hypersensitivity. ***Infections and Infestations:*** *Frequent* - respiratory tract infection (including upper and lower), pneumonia; *Infrequent* - cellulitis, dental caries, vaginitis, vaginal infection, cystitis, vaginal mycosis, eye infection, gastroenteritis, onychomycosis, vaginal candidiasis, otitis media, folliculitis, candidiasis, otitis externa, pyelonephritis, rash pustular; *Rare* - appendicitis, septic shock. ***Injury, Poisoning, and Procedural Complications:*** *Frequent* - fall, skin laceration, contusion, fracture; *Infrequent* - blister, scratch, joint sprain, burn, muscle strain, periorbital haematoma, arthropod bite/sting, head injury, sunburn; *Rare* - joint dislocation, alcohol poisoning, road traffic accident, self mutilation, eye penetration, injury asphyxiation, poisoning, heat exhaustion, heat stroke. ***Investigations:*** *Frequent* - weight decreased, blood creatine phosphokinase increased; *Infrequent* - blood glucose increased, heart rate increased, body temperature increased, alanine aminotransferase increased, blood cholesterol increased, white blood cell count increased, haemoglobin decreased, aspartame aminotransferase increased, blood urea increased, electrocardiogram ST segment abnormal (including depression, elevation), haematocrit decreased, hepatic enzyme increased, blood bilirubin increased, blood glucose decreased, blood creatinine increased, blood alkaline phosphatase increased, blood pressure decreased, blood potassium decreased, blood urine present, electrocardiogram QT corrected interval prolonged; *Rare* - transaminases increased, blood triglycerides increased, blood uric acid increased, cardiac murmur, eosiniphil count increased, neutrophil count increased, platelet count increased, red blood cell count decreased, white blood cell count decreased, white blood cells urine positive, bacteria urine identified, blood lactate dehydrogenase increased, blood potassium increased, neutrophil count decreased, urine output decreased, blood creatine phosphokinase MB increased, ECG signs of myocardial ischemia, electrocardiogram T-wave inversion, heart rate decreased, tuberculin test positive, glucose urine present, glycosylated haemoglobin increased, glucose tolerance decreased, glycosylated haemoglobin decreased, muscle enzyme increased. ***Metabolism and Nutrition Disorders:*** *Frequent* - decreased appetite (including diet refusal, markedly reduced dietary intake), dehydration; *Infrequent* - anorexia, increased appetite, hypercholesterolaemia, hypokalaemia, hyperglycaemia, diabetes mellitus, hypoglycaemia, hyponatremia, diabetes mellitus non-insulin-dependent, hyperlipidaemia, obesity (including overweight), polydipsia; *Rare* - hypertriglyceridaemia, gout, hypernatraemia, weight fluctuation, diabetes mellitus inadequate control. ***Musculoskeletal and Connective Tissue Disorders:*** *Frequent* - musculoskeletal pain (including neck, jaw, chest wall, bone, buttock, groin, flank, musculoskeletal chest, pubic, and sacral), muscle rigidity, muscle cramp; *Infrequent* - muscle twitching, joint swelling, muscle spasms, muscle tightness, arthritis, osteoarthritis, muscular weakness, joint range of motion decreased, sensation of heaviness; *Rare* - tendonitis, osteoporosis, trismus, arthropathy, bursitis, exostosis, night cramps, coccydynia, joint contracture, localised osteoarthritis, osteopenia, rhabdomyolysis, costochondritis, rheumatoid arthritis, torticollis. ***Nervous System Disorders:*** *Frequent* - lethargy, dyskinesia; *Infrequent* - disturbance in attention, parkinsonism, dystonia, drooling, cogwheel rigidity, dysarthria, paraesthesia, hypoaesthesia, loss of consciousness (including depressed level of consciousness), hypersomnia, psychomotor hyperactivity, balance disorder, cerebrovascular accident, hypokinesia, tardive dyskinesia, memory impairment, amnesia, ataxia, dementia, hypotonia, burning sensation, dysgeusia, restless leg syndrome, hypertonia, Parkinson's disease, akinesia, dysphasia, transient ischaemic attack, facial palsy, hemiparesis, myoclonus, sciatica; *Rare* - bradykinesia, coordination abnormal, cognitive disorder, syncope vasovagal, carpal tunnel syndrome, hyporeflexia, intention tremor, muscle contractions involuntary, sleep apnea syndrome, dementia Alzheimer's type, epilepsy, hyperreflexia, mastication disorder, mental impairment, nerve compression, parkinsonian gait, tongue paralysis, aphasia, choreoathetosis, formication, masked facies, neuralgia, paresthesia oral, parkinsonian rest tremor, cerebral haemorrhage, dizziness exertional, hyperaesthesia, haemorrhage intracranial, ischaemic stroke, judgment impaired, subarachnoid haemorrhage. ***Psychiatric Disorders:*** *Frequent* - schizophrenia (including schizoaffective disorder), depression (including depressive symptom), hallucination (including auditory, visual, tactile, mixed, olfactory, and somatic), mood altered (including depressed, euphoric, elevated, and mood swings), paranoia, irritability, suicidal ideation, confusional state, aggression, mania, delusion (including persecutory, perception, somatic, and grandeur); *Infrequent* - tension, nervousness, nightmare, excitability, panic attack (including panic disorder, panic disorder with agoraphobia, and panic reaction), abnormal dreams, apathy, libido decreased, hostility, suicide attempt, bipolar disorder (including bipolar I), libido increased, anger, delirium, acute psychosis, disorientation, bruxism, hypomania, obsessive-compulsive disorder (including obsessive thoughts), mental status changes, crying, dysphoria, completed suicide, flat affect, impulsive behaviour; *Rare* - blunted affect, cognitive deterioration, logorrhea, psychomotor agitation, social avoidant behaviour, psychomotor retardation, suspiciousness, affect lability, anorgasmia, fear, homicidal ideation, tic, premature ejaculation, dysphemia, bradyphrenia, derealisation, depersonalisation. ***Renal and Urinary Disorders:*** *Infrequent* - pollakiuria, dysuria, haematuria, urinary retention, renal failure (including acute and chronic), urinary hesitation, enuresis, nephrolithiasis, micturition urgency, polyuria; *Rare* - nocturia, proteinuria, glycosuria, calculus urinary, azotaemia. ***Reproductive System and Breast Disorders:*** *Infrequent* - erectile dysfunction, vaginal discharge, amenorrhoea, vaginal haemorrhage, menstruation irregular, menorrhagia, premenstrual syndrome, testicular pain, genital pruritus female, ovarian cyst, benign prostatic hyperplasia, prostatitis; *Rare* - gynaecomastia, priapism (including spontaneous penile erection), breast pain, pelvic pain, epididymitis, galactorrhoea, uterine haemorrhage. ***Respiratory, Thoracic, and Mediastinal Disorders:*** *Frequent* - dyspnoea (including exertional); *Infrequent* - sinus congestion, rhinorrhoea, wheezing, epistaxis, asthma, hiccups, productive cough, chronic obstructive airways disease (including exacerbated), rhinitis allergic, pneumonia aspiration, pulmonary congestion, sinus pain, respiratory distress, dry throat, hoarseness; *Rare* - bronchopneumopathy, haemoptysis, respiratory arrest, sneezing, hypoxia, pulmonary embolism, pulmonary oedema (including acute), respiratory failure, brochospasm, nasal dryness, paranasal sinus hypersecretion, pharyngeal erythema, rhonchi, tonsillar hypertrophy, asphyxia, Mendelson's syndrome. ***Skin and Subcutaneous Tissue Disorders:*** *Infrequent* - hyperhydrosis, erythema, pruritis (including generalised), dry skin, decubitus ulcer, dermatitis (including allergic, seborrhoeic, acneiform, exfoliative, bullous, neurodermatitis), ecchymosis, skin ulcer, acne, eczema, hyperkeratosis, swelling face, skin discoloration, photosensitivity reaction, skin irritation, alopecia, rash maculopapular, cold sweat, scab, face oedema, dermal cyst, psoriasis, night sweats, rash erythematous; *Rare* - rash scaly, urticaria, rash maculopapular, rosacea, seborrhoea, periorbital oedema, rash vesicular. ***Vascular Disorders:*** *Frequent* - hypotension; *Infrequent* - hot flush (including flushing), haematoma, deep vein thrombosis, phlebitis; *Rare* - pallor, petechiae, varicose vein, circulatory collapse, haemorrhage, thrombophlebitis, shock.

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole Injection

The following adverse events were reported with aripiprazole injection at doses ≥1 mg/day in clinical trials (749 patients). This list may not include events previously listed elsewhere in the labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening. *Frequent events* are those occurring in at least 1/100 patients; *Infrequent events* are those occurring in 1/100 to 1/1000 patients; *rare events* are those occurring in fewer than 1/1000 patients. ***Ear and Labyrinth Disorders:*** *Infrequent* - hyperacusis. ***General Disorders and Administration Site Conditions:*** *Infrequent* - injection site stinging, abnormal feeling, injection site pruritus, injection site swelling, venipuncture site bruise. ***Infections and Infestations:*** *Infrequent* - bacteruria, urinary tract infection, urosepsis. ***Investigations:*** *Infrequent* - blood pressure abnormal, heart rate irregular, electrocardiogram T-wave abnormal. ***Psychiatric Disorders:*** *Infrequent* - intentional self-injury. ***Respiratory, Thoracic, and Mediastinal Disorders:*** *Infrequent* - pharyngolaryngeal pain, nasal congestion. ***Vascular Disorders:*** *Infrequent* - blood pressure fluctuation.

Postintroduction Reports: Reported since market introduction and temporally (not necessarily causally) related to aripiprazole therapy: allergic reaction (eg, anaphylactic reaction, angioedema, laryngospasm, oropharyngeal spasm, pruritis, or urticaria), grand mal seizure, and jaundice.

DRUG ABUSE AND DEPENDENCE: Aripiprazole is not a controlled substance.

Abuse and Dependence: Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Patients should be evaluated carefully for a history of drug abuse and closely observed for signs of ABILIFY (aripiprazole) misuse or abuse.

OVERDOSAGE: 76 cases of deliberate or accidental overdosage with oral ABILIFY alone or in combination with other substances were reported worldwide [44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (mydriasis and feeling abnormal)]. Additionally, 10 of these cases were in children (age 12 and younger) involving oral aripiprazole ingestions up to 195 mg with no fatalities. The largest known acute ingestion was 1080 mg of oral aripiprazole (36 times maximum recommended daily dose) in a patient who fully recovered. Common adverse events (reported in at least 5% of all overdose cases) were vomiting, somnolence, and tremor. **For more information on symptoms of overdose, see Full Prescribing Information.**

Management of Overdosage: No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and, if QTc interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers. ***Charcoal:*** In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%. ***Hemodialysis:*** Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
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Otsuka America Pharmaceutical, Inc.
Rockville, MD 20850 U.S.A.

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Knowledge transforms, illuminates, and unlocks the door to the science of mental illness. Over the past 30 years, UPMC's Western Psychiatric Institute and Clinic (WPIC) has set the standard for innovative clinical care including pioneering short- and long-term treatment approaches. We have incorporated both pharmacologic and psychotherapeutic regimens that are standards of care in behavioral health today. As the number one recipient of federal psychiatric research funding and with a history of clinical advances, our psychiatrists' findings have informed their colleagues' practices across the country. WPIC clinicians and researchers have shed light on mental illness across the lifespan and have created new tools for managing pervasive developmental disorders, addictions, mood and anxiety disorders, geriatric psychiatry, and eating disorders. Our specialized clinical programs tackle the most complex cases, with teams who specialize in psychiatry, psychopharmacology, clinical psychology, and neurology assessing and crafting complete, individualized procedure plans. WPIC psychiatrists provide treatment based on current scientific advances so those with mental illness can live healthier and more productive lives.

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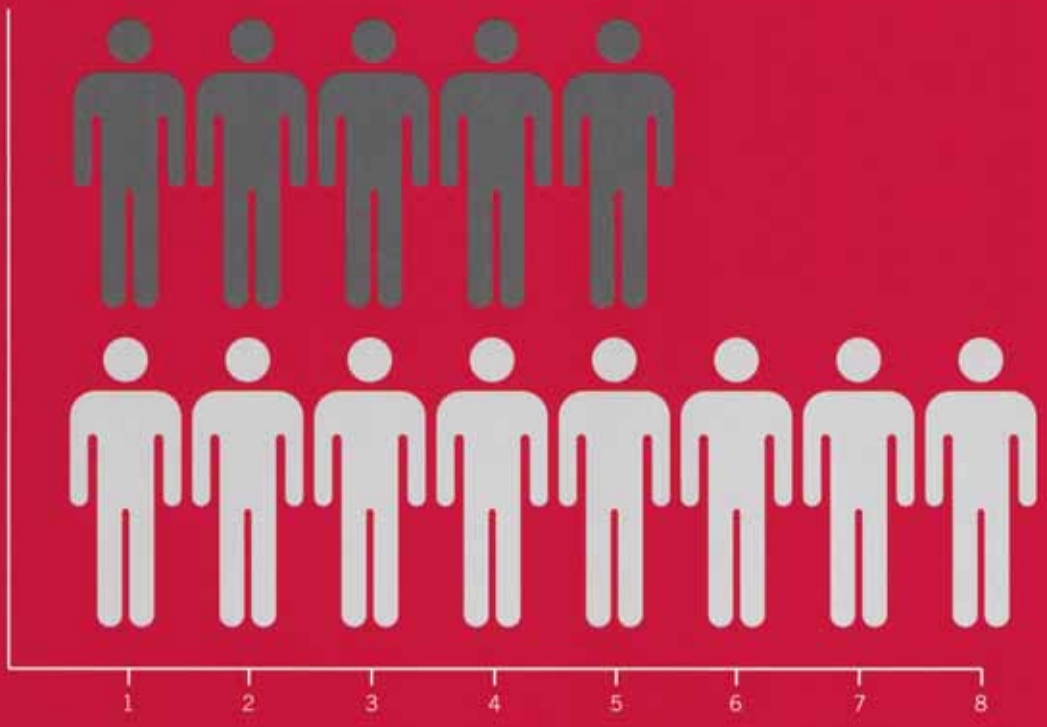

People with severe mental illness die up to 3 decades earlier, on average, than the general population.[1,2]

Be aware.
Screen and monitor your patients.
Make a difference.

Pfizer

KNOWTHEFACTS

Heart disease is a leading cause of death in patients with severe mental illness.[1,2]

Major risk factors include[3]

- Weight gain
- Diabetes
- High blood pressure
- High cholesterol
- Smoking

Be aware.
Screen and monitor your patients.
Make a difference.

References: 1. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis* [serial online]. 2006 April;3(2). Available at: http://www.cdc.gov/pcd/issues/2006/apr/05_0180.htm. Accessed December 7, 2006. **2.** Miller BJ, Paschall CB III, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. *Psychiatr Serv.* 2006;57:1482-1487. **3.** *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Executive Summary.* Bethesda, Md: National Institutes of Health, National Heart, Lung, and Blood Institute; 2001. NIH publication 01-3670.

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Still depressed?
Anxiety, insomnia, low energy
Currently on an SSRI
Still suffering
It may be time to make a change

IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

- EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI; at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.

Please see brief summary of Prescribing Information on adjacent pages.

Break the Cycle

with EFFEXOR XR

- In an open-label study of patients who failed previous antidepressant treatment, nearly **60%** achieved remission when changed to EFFEXOR XR[1]
- In the **PREVENT**™ study, the probability of preventing a new episode of depression was **92%** with EFFEXOR XR in maintenance year 2 vs. 55% with placebo[2*]
- More than **12** years of clinical experience and over **20** million patients treated with EFFEXOR/EFFEXOR XR[3†]

- Adult and pediatric patients with MDD can experience worsening of their depression and/or the emergence of suicidal ideation and behavior, whether or not they are taking antidepressants. **Patients treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms.
- The development of potentially life-threatening serotonin syndrome may occur when EFFEXOR XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems. Concomitant use of EFFEXOR XR with MAOIs is contraindicated. If concomitant use of EFFEXOR XR with an SSRI, SNRI, or a triptan is clinically warranted, careful observation of the patient is advised. Concomitant use of EFFEXOR XR with tryptophan supplements is not recommended.
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.
- Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. See the Precautions section of the Prescribing Information.
- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled MDD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence ≥10% and ≥2x that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

*For study design, please see references or visit **PreventStudy.com**.

†Based on IMS National Prescription Audit and SDI longitudinal prescription data.

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EFFEXOR XR® *EXTENDED RELEASE CAPSULES*

The change they deserve.

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is a unique patient support and education program that is designed to help you foster successful therapy

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offers patients access to a call center to speak with a health care provider for patient support and education to reinforce your efforts

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supplies feedback and updates about these patient calls to you, their physician

Encourage your **EFFEXOR XR** patients to enroll in ***Dialogues*** by calling **866-313-3737** — and you can visit **mddpatientsupport.com**

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EFFEXOR XR® EXTENDED RELEASE CAPSULES

The change they deserve.

References: 1. Baldomero EB, Ubago JG, Cercós CL, et al. Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. *Depress Anxiety.* 2005;22:68-76. **2.** Data on file, Wyeth Pharmaceuticals Inc. A randomized, multicenter, double-blind, placebo-controlled study (N=1,096 adults). This trial included an acute, a continuation, and 2 one-year maintenance phases. At the start of each of the 2 maintenance phases, EFFEXOR XR responders were re-randomized to either EFFEXOR XR or placebo. The primary end point was time to recurrence of depression. **3.** Data on file, Wyeth Pharmaceuticals Inc.

Please see brief summary of Prescribing Information on adjacent pages.

Wyeth®

122873-01 January 2007

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EFFEXOR XR® EXTENDED RELEASE CAPSULES

BRIEF SUMMARY. See package insert for full prescribing information.

Suicidality in Children and Adolescents

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings and Precautions: Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with Major Depressive Disorder (MDD), obsessive-compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4,400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). **WARNINGS: Clinical Worsening and Suicide Risk**—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders. It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults. **All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Adults with MDD or comorbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD and other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). **Families and caregivers of pediatric patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised. **Screening Patients for Bipolar Disorder**: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. Prior to initiating antidepressant treatment, patients with depressive symptoms should be screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Effexor XR is not approved for use in treating bipolar depression. **Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Serotonin Syndrome**—The development of potentially life-threatening serotonin syndrome may occur with Effexor XR treatment, particularly with (i) concomitant use of serotonergic drugs and (ii) with drugs that impair metabolism of serotonin (see **CONTRAINDICATIONS—MAOIs**). If concomitant treatment of Effexor XR with an SSRI, SNRI, or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with serotonin precursors (such as tryptophan supplements) is not recommended. **Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. **Mydriasis**—Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). **PRECAUTIONS: General—*Discontinuation of Treatment with Effexor XR.*** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. ***Insomnia and Nervousness***: Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 1% of both depressed patients and Panic Disorder (PD) patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0% of SAD and PD patients. ***Changes in Weight: Adult Patients***: In short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In 12-week SAD trials, 3% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had ≥7% loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. ***Pediatric Patients***: Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% of Effexor XR patients vs. 3.6% of placebo patients; $P<0.001$) and the SAD study (47% of Effexor XR patients vs. 14% of placebo patients; $P<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month MDD study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Height: Pediatric Patients***: In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while placebo patients grew an average of 1.0 cm (n=132); $P=0.041$. This difference in height increase was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). During the 16-week, placebo-controlled SAD study, both the Effexor XR (n=109) and the placebo (n=112) patients grew an average of 1.0 cm. In the 6-month MDD study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Appetite: Adult Patients***: Treatment-emergent anorexia was more commonly reported for

Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. ***Pediatric Patients***: Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. In the placebo-controlled trial for SAD, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Effexor XR and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Effexor XR and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo. ***Activation of Mania/Hypomania***: Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. ***Hyponatremia***: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. ***Seizures***: In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. ***Abnormal Bleeding***: Abnormal bleeding (most commonly ecchymosis) has been reported. ***Serum Cholesterol Elevation***: Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. ***Use in Patients With Concomitant Illness***: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient *Medication Guide About Using Antidepressants in Children and Teenagers* is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients 1) about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities; 2) to avoid alcohol while taking Effexor XR; and 3) about the risk of serotonin syndrome with the concomitant use of Effexor XR and triptans, tramadol, tryptophan supplements, or other serotonergic agents. Patients should be advised to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations and nutritional supplements they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena; or 4) if they have a history of glaucoma or increased intraocular pressure. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions**—***Alcohol***: A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine***: Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam***: A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol***: Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. ***Lithium***: A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. ***Drugs Highly Bound to Plasma Proteins***: Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. ***Drugs That Inhibit Cytochrome P450 Isoenzymes***: CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. ***Drugs Metabolized by Cytochrome P450 Isoenzymes***: Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. ***Imipramine***: Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. ***Risperidone***: Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4**: Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. ***Indinavir***: In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2**: Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9**: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19**: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). ***MAOIs***: See **CONTRAINDICATIONS** and **WARNINGS**. ***CNS-Active Drugs***: Use caution with concomitant use of venlafaxine and other CNS-active drugs. **Serotonergic Drugs and Triptans (see WARNINGS: Serotonin Syndrome):** Based on the mechanism of action of Effexor XR and the potential for serotonin syndrome, caution is advised when Effexor XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's wort. If concomitant treatment of Effexor XR with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with tryptophan supplements is not recommended. ***Electroconvulsive Therapy (ECT)***: There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—***Carcinogenesis***: There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. ***Mutagenesis***: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. ***Impairment of Fertility***: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m^2 basis. **Pregnancy**—***Teratogenic Effects***—***Pregnancy Category C***. Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m^2 basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. ***Nonteratogenic Effects***: Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS**: ***Associated with Discontinuation of Treatment***—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD***—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. ***Vital Sign Changes***: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). ***Laboratory Changes***: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. ***Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR***—N=6,670. "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease (including pulmonary eosinophilia), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C025, revised August 2006.

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PSYCHIATRIST

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Rose Mary Boustany, MD, Chairperson
Abu-Haydar Neuroscience Institute and
Acting Chairperson
American University of Beirut
P.O.Box 11-0236 - Riad El-Solh/Beirut 1107-2020, Lebanon
E-mail submission is also encouraged at: rb50@aub.edu.lb

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Federal Medical Center
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ciwuagwu@bop.gov or mmwilson@bop.gov

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– email <jzwerin@dmhnsh.state.ca.us>
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DARTMOUTH MEDICAL SCHOOL. The Department of Psychiatry is seeking a senior faculty member to serve as Medical Director of New Hampshire Hospital, in Concord, NH.

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The NHH Medical Director will serve as the chief clinical officer of New Hampshire Hospital. The NHH Medical Director is part of the Senior Leadership of the Department of Psychiatry and will work closely with the Chair to lead the Department and to further extend the established state-academic partnership. The role will include supporting and facilitating excellent clinical care, supporting New Hampshire Hospital's function as an outstanding teaching and training site, and facilitating research activities that serve the mission of both New Hampshire Hospital and the Department.

The ideal candidate will have a passion for public sector care, a patient-centered clinical orientation, excellent clinical leadership skills, sound interpersonal skills, administrative experience, and a strong academic background. The candidate must be a board certified psychiatrist.

Curriculum vitae and three letters of reference should be sent to:

Alan I. Green, M.D., Raymond Sobel Professor and Chairman
Department of Psychiatry, Dartmouth-Hitchcock Medical Center
1 Medical Center Drive, Lebanon, NH 03756

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For more information about the MIND Institute, as well as a complete description of the opportunities available, please visit our website at:
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PSYCHIATRISTS

The Department of Veterans Affairs, Central Texas Veterans Health Care System (CTVHCS), is accepting applications for several positions for board-certified Psychiatrists at Temple and Waco, Texas. CTVHCS is affiliated with the Texas A&M University Health Science Center. Applicants with interest in teaching and research will be given preference. CTVHCS offers competitive salaries and excellent benefits.

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Reply to: Michael Serby, MD, Associate Chairman, Department of Psychiatry, Beth Israel Medical Center, 1st Avenue at 16th Street, NY, NY 10003, Fax 212-420-3442. Email: mserby@bethisraelny.org.

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Harvard Medical School and Brigham and Women's/Faulkner Hospitals are seeking an academic leader to serve as the Stanley Cobb Professor of Psychiatry and the Chairperson of the Department of Psychiatry at Brigham and Women's/Faulkner Hospitals, a founding member of the Partners HealthCare System. This individual will be responsible for the full scope of clinical, research and educational activities of the department as well as collaborative activities with the other departments of this academic medical center, Partners HealthCare System, Harvard Medical School, Faulkner Hospital and other affiliated institutions.

Candidates should have a strong record as a mentor and as a teacher, national recognition for psychiatric research accomplishments, and possess exceptional leadership, managerial, and collaborative skills. Ideally, she/he would be a proven academic medical leader with an international reputation in one of the disciplines of psychiatry, who can lead a complex and successful organization to even higher levels of excellence.

Martin A. Samuels, MD, Chairman, Department of Neurology
Brigham and Women's Hospital
Professor of Neurology, Chair, Search Committee
c/o Wanda McClain, Brigham and Women's Hospital
75 Francis Street PB411, Boston, MA 02115
Email: BWHPsychSearch@partners.org

Interested candidates are requested to submit a current Curriculum Vitae by email to BWHPsychSearch@partners.org by May 15, 2007 for consideration.

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ALEXANDRIA Strong clinical skills. Prefer experience in Geropsychiatry, Substance Abuse and/or PTSD. CV/Application to tammie.arnold@med.va.gov or Tammie Arnold, Psychiatry Service (116), P.O. Box 69004, Alexandria, LA 71306-9004. (318) 473-0010 ext 2696.

SHREVEPORT Prefer experience in Substance Abuse, PTSD. Contact Tracie Bennett at (318) 221-8411, ext 5118 or tracie.bennett@va.gov. Email or mail your CV to VAMC, HRMS (05) TB, 510 E. Stoner Ave, Shreveport, LA. (318) 221-8411, ext 5118.

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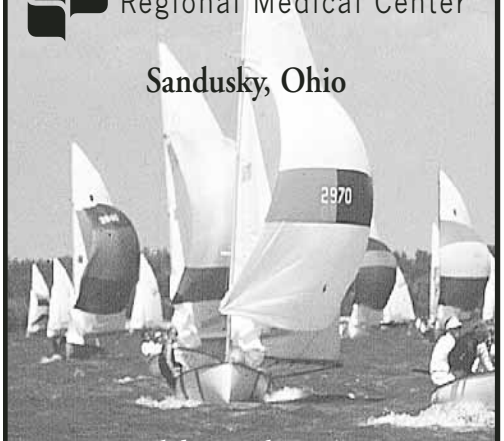

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BRIEF SUMMARY. See package insert for full prescribing information.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. GEODON (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

INDICATIONS—GEODON Capsules is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. GEODON® (ziprasidone mesylate) for Injection is indicated for acute agitation in schizophrenic patients.

CONTRAINDICATIONS — ***QT Prolongation:*** Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS—Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning).** ***QT Prolongation and Risk of Sudden Death:*** **GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT_c prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec.** ***Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. 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 (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS —** ***General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis)**. Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. 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 in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine,* 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole,* a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. *Cimetidine,* 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives,* ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan,* a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS —** ***Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** 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. Schizophrenia: Body as a Whole — *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System — *Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System — *Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine — *Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders — *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hyperkalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System — *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System — *Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, bucconglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System — *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages — *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses —*Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System —*Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE —** ***Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/75).

References: 1. Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. *Psychopharmacology*. 2001;155:128-134. **2.** Brook S, Walden J, Benattia I, Siu CO, Romano SJ. Ziprasidone and haloperidol in the treatment of acute exacerbation of schizophrenia and schizoaffective disorder: comparison of intramuscular and oral formulations in a 6-week, randomized, blinded-assessment study. *Psychopharmacology*. 2005;178:514-523. **3.** Lesem MD, Zajecka JM, Swift RH, Reeves KR, Harrigan EP. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. *J Clin Psychiatry*. 2001;62:12-18. **4.** Brook S, Lucey JV, Gunn KP, for the Ziprasidone IM Study Group. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. *J Clin Psychiatry*. 2000;61:933-941.

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Control acute agitation with

GEODON®

for ***Injection*** *(ziprasidone mesylate)*

In schizophrenia…

Rapid improvement with low EPS[1,2]

- Significant control achieved between 15 and 30 minutes* after injection[1,3]
- Proven advantages over haloperidol IM
  - twice the improvement as measured on the BPRS[4†]
  - significantly lower incidence of movement disorders[2‡]
- Smooth transition, with continued improvement, from IM to oral therapy[2,4]
- May be used concomitantly with benzodiazepines

*In 2 pivotal studies vs control, significance was achieved at 15 minutes (with 10 mg dose) and 30 minutes (with 20 mg dose), respectively.

†In a 7-day, open-label IM-to-oral transition study.

‡In a 6-week, open-label IM-to-oral transition study.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT_C interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first.

In fixed-dose, pivotal studies, the most commonly observed adverse events associated with the use of GEODON for Injection (incidence ≥5%) and observed at a rate in the higher GEODON dose groups (10 mg, 20 mg) of at least twice that of the lowest GEODON dose group (2 mg control) were somnolence (20%), headache (13%), and nausea (12%).

Please see brief summary of prescribing information on adjacent page.