Anxiety disorders often other comorbid conditions

In patients with **social anxiety disorder (SAD)** and a comorbid psychiatric disorder...

In a study, SAD preceded the disorder in more than 75% of cases³

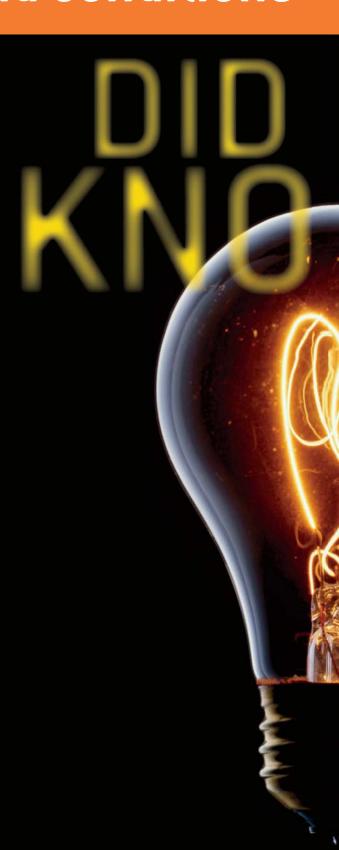
Facts about SAD

- One of the most common anxiety disorders¹
- Affects approximately 15 million American adults—about the same amount affected by major depressive disorder¹
- A lifetime prevalence of over 13%4
- Frequently not identified⁵

SAD patients have an increased risk of developing³:

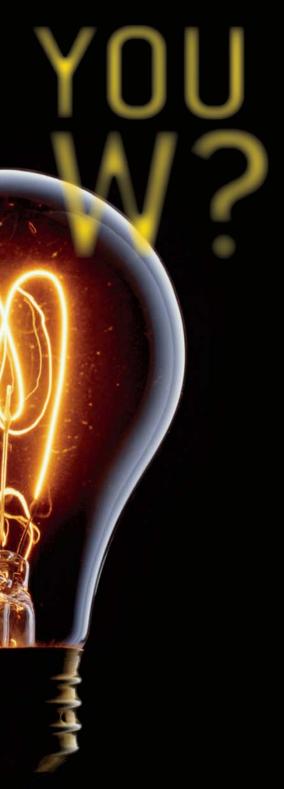
- Obsessive compulsive disorder
- Major depressive disorder
- Panic disorder
- Drug and alcohol dependency

References: 1. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:617-627. 2. National Institute of Mental Health. The Numbers Count: Mental Disorders In America. http://www.nimh.nih.gov/publicat/numbers.cfm#MajorDepressive. Accessed August 30, 2007. **3.** Schneier FR, Johnson J, Hornig CD, Liebowitz MR, Weissman MM. Social phobia: comorbidity and morbidity in an epidemiologic sample. Arch Gen Psychiatry. 1992;49:282-288. 4. Magee WJ, Eaton WW, Wittchen H-U, McGonagle KA, Kessler RC. Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. Arch Gen Psychiatry. 1996;53:159-168. **5.** Connor KM, Kobak KA, Churchill LE, Katzelnick D, Davidson JRT. Mini-Spin: a brief screening assessment for generalized social anxiety disorder. Depress Anxiety. 2001;14:137-140. 6. Abramowitz JS, Storch EA, Keeley M, Cordell E. Obsessive-compulsive disorder with comorbid major depression: what is the role of cognitive factors? Behav Res Ther. In press. 7. Obsessive-Compulsive Disorder. In: Sadock BJ, Sadock VA, eds. Synopsis of Psychiatry. 9th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:616-623. 8. Obsessive-Compulsive Disorder. In: Hales RE, Yudofsky SC, Talbott JA, eds. Textbook of Psychiatry. 3rd ed. Washington, DC: American Psychiatric Press, Inc. 1999:600-610. 9. American Psychiatric Association. Practice guideline for the treatment of patients with obsessive-compulsive disorder. http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm. Accessed August 21, 2007.



present first, before

AFFECTING MORE THAN 40 MILLION AMERICAN ADULTS EACH YEAR²



In patients with obsessive compulsive disorder (OCD) and comorbid depression...

OCD preceded the disorder, suggesting that mood disturbances may occur as a response to the functional impairment of OCD⁶

Facts about OCD

- Affects about 2.2 million American adults¹
- 67% of patients will have an associated lifetime diagnosis of major depressive disorder
- Can be misdiagnosed as depression, psychosis, phobias, or personality disorder⁸

OCD symptoms can be accompanied by:

- Eating disorders
- Other anxiety disorders
- Major depressive disorder
- Alcohol or drug abuse

Early recognition and treatment of anxiety disorders are an important part of successful therapy



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Now, 3-day practice orals course limited to 20 students

- Opening sessions will teach oral exam skills
- ◆ Fees include doing two practice oral exams
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Nov 17-18 – San Francisco February 16-19, 2008 – Tampa

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When you positively must pass

The Seventh Annual Pharmacogenetics in Psychiatry Meeting

April 4 – 5, 2008 New York Marriott Marquis Hotel – New York, NY



THE PROGRAM

The Seventh Annual Pharmacogenetics in Psychiatry meeting will include sessions presenting the latest pharmacogenetics data from around the world. Topics to be discussed include: prediction of clinical response to antipsychotic and antidepressant drugs; genes associated with the development of adverse side effects; novel statistical approaches; and the implication of whole genome association approaches for pharmacogenetics.

ABSTRACTS

Abstracts are invited for oral or poster presentation. Abstracts should include a title of the presentation, the authors' names and affiliations, and no more than 250 words of text. Submissions should indicate the corresponding author's e-mail address, telephone and fax numbers and whether an oral or poster presentation is preferred.

ABSTRACT SUBMISSION

Deadline: January 25, 2008

E-Mail abstracts in Microsoft Word or Word Perfect format

Abstracts

E-Mail: Patricia Raikos praikos@nshs.edu Phone: (718) 470.8418 FAX: (718) 343.1659

Conference Information

E-Mail: Rick Hostnik rhostnik@nshs.edu Phone: (516) 465.2500 FAX: (516) 465.8204

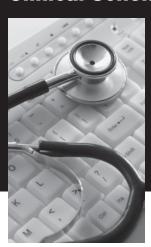
www.pharmacogeneticsinpsychiatry.com



11058E-10-07

2007-2008 Call for Applications

Robert Wood Johnson Foundation **Clinical Scholars**



The Robert Wood Johnson Foundation Clinical Scholars program fosters the development of physician leaders who will transform health and health care in this country. Each year the program selects a new class of top physicians from across the country to learn critical skills and gain high-level contacts with some of the most dynamic and accomplished leaders in the health care field.

Scholars are placed for two to three years at one of four prestigious

training sites and receive full financial support, including annual stipends and funds for research and professional travel. Applicants must be citizens or permanent residents of the United States or its territories and must have completed the clinical requirements of their residency/fellowship training by the date of entry into the program (except for surgeons). Scholars may not hold appointments as subspecialty fellows during their tenure in the program.

Application Deadline

February 29, 2008

The complete call for applications is available both on the Foundation's Web site at www.rwjf.org/cfp/clinicalscholars and the program's Web site at http://rwjcsp.unc.edu or by calling (919) 843-1351.

Robert Wood Johnson Foundation

Robert Wood Johnson Foundation Clinical Scholars is a national program of the Robert Wood Johnson Foundation.

About the Robert Wood Johnson Foundation

The Robert Wood Johnson Foundation focuses on the pressing health and health care issues facing our country. As the nation's largest philanthropy devoted exclusively to improving the health and health care of all Americans, the Foundation works with a diverse group of organizations and individuals to identify solutions and achieve comprehensive, meaningful and timely change.

For more than 35 years the Foundation has brought experience, commitment and a rigorous, balanced approach to the problems that affect the health and health care of those it serves. When it comes to helping Americans lead healthier lives and get the care they need, the Foundation expects to make a difference in your lifetime.

For more information visit www.rwjf.org



Important Safety Information

- Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders.
- Patients of all ages started on therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Cymbalta is not approved for use in pediatric patients.

Cymbalta should not be used concomitantly with monoamine oxidase inhibitors (MAOIs) or thioridazine and not in patients with a known hypersensitivity or with uncontrolled narrow-angle glaucoma.

Clinical worsening and suicide risk: All patients being treated with an antidepressant for any indication should be monitored appropriately and

observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially within the first few months of treatment and when changing the dose. A health professional should be immediately notified if the depression is persistently worse or there are symptoms that are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication.

Development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs, including triptans. Concomitant use is not recommended.

Cymbalta should not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (CrCl <30 mL/min).

Postmarketing, severe elevations of liver enzymes or liver injury with a hepatocellular, cholestatic, or mixed pattern have been reported.

Cymbalta should generally not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Milestones reached since coming to market in 2004:

5 million patients treated in the United States1

20 million prescriptions written²

Over 298,000 prescribing physicians³

Fastest-growing antidepressant in 20064 and to date in 20075*

Helping you help your patients, one at a time.

Cases of orthostatic hypotension and/or syncope as well as cases of hyponatremia have been reported.

As observed in DPNP clinical trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases up to 52 weeks, an increase in HbA $_{\rm lc}$ in both the Cymbalta (0.5%) and routine care groups (0.2%) was noted.

Most common adverse events (≥5% and at least twice placebo) in premarketing clinical trials were:

MDD: nausea, dry mouth, constipation, fatigue, decreased appetite, somnolence, and increased sweating. DPNP: nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia. GAD: nausea, fatigue, dry mouth, somnolence, constipation, insomnia, appetite decreased, increased sweating, libido decreased, vomiting, ejaculation delayed, and erectile dysfunction.

See Brief Summary of full Prescribing Information, including Boxed Warning, on following spread.

DD47513 1007 PRINTED IN USA © 2007, ELI LILLY AND COMPANY. ALL RIGHTS RESERVED. Cymbalta is a registered trademark of Eli Lilly and Company.

References: 1. Lilly Global Product Safety, January 2007.

- 2. IMS Health, May 2007.
- 3. IMS Health, March 2007.
- 4. IMS, National Prescription data, January 2007.
- **5.** IMS, National Prescription data, July 2007.

 $\mbox{*}$ Data current as of July 2007.





(duloxetine hydrochloride) Delaved-release Capsules

Brief Summary: Consult the package insert for complete prescribing information.

WARNING

WARNING

WARNING

Suicidality and Antidepressant Drugs-Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in exhibit, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with suitidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with suitidepressants compared to placebo in adults increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and 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. Cymbalta is not approved for use in pediatric patients.

INDICATIONS AND USAGE: Cymbalta is indicated for the: treatment of major depressive disorder (MDD); the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN); treatment of generalized anxiety disorder (GAD)

CONTRAINDICATIONS: Hypersensitivity—Known hypersensitivity to duloxetine or any of the inactive ingredients. Monoamine Oxidase Inhibitors (MAOIs)—Concomitant use with Cymbalta is contraindicated (see WARNINGS). Uncontrolled Narrow-nagle Glaucoma—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use is not recommended in patients with uncontrolled narrow-angle glaucoma.

mydriasis; therefore, its use is not recommended in patients with uncontrolled narrow-angle glaucoma.

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. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed these drugs increase the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 55 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive datol of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 77,000 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 25 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. The p

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated			
	Increases Compared to Placebo			
<18	14 additional cases			
18-24	5 additional cases			
	Decreases Compared to Placebo			
25-64	1 fewer case			
≥65	6 fewer cases			

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not

sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of

there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and 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.

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 MDD as well as for other indications, both psychiatric and nonpsychiatric Athbough 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. emerging suicidality

emerging sucutarity.

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, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUTIONS, Discontinuation can be associated with certain symptoms (see PRECAUT

of Treatment with Cymbalta)

of Treatment with Cymbalta).

Families and caregivers of 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 Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

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, includiating a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta (duloxetine) is not a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta (duloxetine) is not approved for use in treating bipolar depression.

approved for use in treating bipolar depression.

MAOIS—In patients receiving a serotonin reuptake inhibitor (SSRI) in combination with an MAOI, there have been reports of serious, sometimes Ital. 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 SSRIs and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Cymbalta and MAOIs have not been evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI. Sorotonin Syndrome—The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms way include mental status changes (eg. agitation, hallucinations, coma), autonomic instability (eg. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg. hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg. hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg. hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg.

Injuring the image is a continuous data abertations (eg., hypertenexia, incordination) among systemicisman symptoms (eg., nausea, vomiting, diarrhea).

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS and WARNINGS, Potential for Interaction with MAOIs).

If concomitant treatment of Cymbalta 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 Cymbalta with serotonin precursors (such as tryptophan) is not recommended (see PRECAUTIONS, Drug Interactions).

PRECAUTIONS, Grug Interactions).

PRECAUTIONS: General—Hepatotoxicity—Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) almost the upper limit of normal occurred in 1% (38/3732) of Cymbalta-treated patients compared to 0.2% (6/2568) of placebo-treated patients. In placebo-crontrolled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal and >5 times the upper limit of normal selvels to more than thenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is glentaly recognized as an important predictor of severe liver injury, In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may account to expect the control of the con placeo-treated patients also flad transminases elevations with elevated transminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Orghostatic Hypotension and Syncope—Orthostatic hypotension flower and the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as anthypertensives) or are potent CVP142 inhibitors (see CLINICAL PHARMACOLOGY, Drug-Drug Interactions, and PRECAUTIONS, Drug Interactions) and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy. Effect on Blood Pressure—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure at doses up occurred at a rate greater than or equal to 1% and at a significantly higher rate in unoxeme-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; nightmares; insomnia; diarrhea; anxiety; hyperhidrosis; and vertigo.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been

occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo circizeness, nausea, headache, paresthesia, vomiting, irritability, nightnares; insomnia; diarrhea; anxiety, Phyperhidrosis; and vertigo.

During marketing of other SSRIs and SMRIs (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, apitation, dizziness, sensory disturbances (e.g. paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional tability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the obese 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.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric morbidity may have on the stability of Cymbalta's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with concomitant and the control of the patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. As observed in DPNP triaks, Cymbalta are recent history of myocardial infarction or unstable coronary artery disease.

Patients with these diagnoses were generally excluded from clinical studies u

Serotonin Syndrome). The concomitant use of Cymbalta 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 Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS, Serotonin Syndrome). Potential for Interaction with Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal pract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydroylsis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emplying (eg. some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum— and magnesium-containing antacids (51 mEq) or Cymbalta with tamotidine, had no significant effect on the rate or extent of duloxetine absorption.

Monoamine Oxidase Inhibitors—See CONTRAINDICATIONS and WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertifity—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years. In temale mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose (MIRH). 60 mg/day) and 6 times the human dose of 120 mg/day on a mg/m² basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis) did not increase the incidence of tumors. Mutagenesis—Duloxetine was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m² basis) did not increase the incid

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

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs),

Iter 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, hypotonia, hypertenia, 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, Monoamine Oxidase). Intal, in some cases, are clinical picture is consistent with Serotomin Syndrome (see WARNINGS, Mondamine Oxidase Inhibitors). When treating a pregnant woman with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, particip while an Cymbalth is not recompanded.

nursing while on Cymbalta is not recommended.

Pediatric Use—Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS, Clinical Worsening and Suicide Risk). Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

must balance the potential risks with the clinical need.

Geriatric Use—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN premarketing studies, 33% (357) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPN studies, 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 greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, Cymbalta has been associated with cases of clinically significant hyponatremia (see Hyponatremia, under PRECAUTIONS).

ADVERSE REACTIONS: Cymbalta has been evaluated for safety in 2418 patients diagnosed with MDD who participated ADVERSE REACTIONS: Cymbalta has been evaluated for safety in 2418 patients diagnosed with MDD who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 Cymbalta-treated patients, 1139 patients participated in eight 8 or 9 week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated patients were exposed for at least 1 year. Cymbalta has also been evaluated for safety in 45 patients with diabetic peripheral neuropathy representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated patients, 568 patients participated in two 12 to 13 week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with placebo, were exposed to Cymbalta for up to 12 months at 60 mg twice day in an extension hasse. Amont these 1074 clients, safety for a furtation of 8 months of excosure to Cymbalta and 220 Patients. 491 months at 60 mg twice day in an extension hasse. Amont these 1074 clients. 484 had 6 months of exosure to Cymbalta and 220 Patients. in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had 12 months

Cymbalta has also been evaluated for safety in 668 patients with GAD representing 95 patient-years of exposure

Cymballa flas also been evaluated for Safety in bolo patients with GAD representing 95 patient-years of exposure. These 668 patients participated in 9- or 10-week placebo-controlled trials at doses ranging from 60 to 120 mg once daily. Of these 668 patients, 449 were exposed for at least 2 months to Cymbalta. In the full cohort of placebo-controlled clinical trials for any indication, safety has been evaluated in 8504 patients treated with placebo. In clinical trials, a total of 23,983 patients have been exposed to duloxetine. In duloxetine clinical trials, adverse reactions were assessed by collecting adverse events, results

exposed to dutosemile. In dutoxenile unlined trials, adverse reactions were assessed by concerning currence events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping similar types of events into a smaller number of standardized event categories is necessary. MedDRA terminology was used to classify reported adverse events.

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. Events reported during the studies were necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

**Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major

Depressive Disorder—Approximately 10% of the 1139 patients who received Cymbalta in the MDD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausor (Cymbalta 1 4%, placebo 1.01%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbaltat-treated patients and at a rate of at least twice that of placebo). <u>Diabetic Peripheral Neuropathic Palm</u>—Approximately 14% of the 568 patients who received Cymbalta in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients receiving placebo. Nausea (Cymbalta 3.5%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0.4%) and fatigue (Cymbalta 1.1%, placebo 0.4%) ever the common adverse events reported as reasons for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo). <u>Generalized Anxiety Disorder</u> Approximately 16% of the 658 patients who received Cymbalta in the GAD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 495 patients receiving placebo. Nausea (Cymbalta 3.7%, placebo 0.2%), vomiting (Cymbalta 1.4%, placebo 0%), and dizziness (Cymbalta 1.2%, placebo 0.2%) events reported as reasons for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo.

**Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta Treated Patients in Placebo-Controlled Trials—Major Depressive Disorder—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of MDD placebo-controlled trials (N=1139 Cymbalta;

N=777 placebo) with an incidence greater than placebo were: <u>Gastrointestinal Disorders</u>—nausea, dry mouth, constipation, diarrhea, vomiting; <u>Metabolism and Nutrition Disorders</u>—appetite decreased (includes anorexia); <u>Investigations</u>—weight decreased; <u>General Disorders</u> and <u>Administration Site Conditions</u>—fatigue; <u>Nervous System Disorders</u>—dizziness, somnolence, tremors; <u>Skin and Subcutaneous Tissue Disorders</u>—weating increased; <u>Vascular Disorders</u>—insomnia (includes anionsomia), anxiety, libido decreased, organs abnormal (includes aniongamia); <u>Reproductive System and Breast Disorders</u>—males only: erectile dysfunction, ejaculation delayed, ejaculatory dysfunction (includes ejaculation disorder and ejaculation disorder and ejaculation failure).

ejaculation failure). The following events were reported by at least 2% of patients treated with Cymbalta for MDD and had an incidence
≤ placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough,
nasopharyngitis, and upper respiratory tract infection.
The most commonly observed adverse events in Cymbalta-treated MDD patients (incidence ≥5% and at least twice
the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating.

increased sweating.

Diabetic Peripheral Neuropathic Pain—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPN placebo-controlled trials (N=225 Cymbalta 60 mg BID; N=228 Cymbalta 60 mg BID; N=228

the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia.

<u>Generalized Anxiety Disorder</u>—Treatment-emergent adverse events that occurred in 2% or more of patients treated Generalized Anxiety Disorder—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of GAD placebo-controlled trials (doses of 66-120 moce daily) (N=668 Cymbalta; N=495 placebo) and with an incidence greater than placebo were: Eye Disorders—vision blurred; Gastrointestinal Disorders—anausea, dry mouth, constipation, diarrhea, vomiting, abdominal pain, dyspepsia; General Disorders—and Administration Site Conditions—fatigue; Metabolism and Nutrition Disorders—insomnia, libid decreased, administration Site Conditions—fatigue; Wetabolism and Nutrition Disorders—insomnia, libid decreased, administration shormal; Reproductive System and Breast Disorders—ejaculation dedy, erectile dysfunction; Bespiratory. Thoracic and Mediastinal Disorders—yawning; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—of flushes.

The following events were reported by at least 2% of patients treated with Cymbalta for GAD and had an incidence ≤ placebo: nasopharyngitis, upper respiratory tract infection, heachache, pollakiuria, and musculoskeletal pain (includes myalgia, neck pain).

makes makes pain).

The most commonly observed adverse events in Cymbalta-treated GAD patients (incidence ≥5% and at least twice

the incidence in placebo patients) were: nausea; fatigue; dry mouth; somnolence; constipation; insomnia; appetite decreased; hyperhidrosis; libido decreased; vomiting; ejaculation delayed; and erectile dysfunction. Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of Cymbalta did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from

Effects on Male and Female Sexual Function—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. Reliable estimates of the incidence and severify of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be refuctant 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. Sexual side effects spontaneously reported by at least 2% of either male or female patients taking Cymbalta in MDD placebo-controlled trials were: Males (N=378 Cymbalta; N=247 placebo): orgasm abnormal (includes anorgasmia), ejaculatory dysfunction (includes ejaculation disorder and ejaculation failure), libido decreased, erectile dysfunction, ejaculation delayed. Females (N=761 Cymbalta; N=530 placebo): orgasm abnormal

libido decreased.

Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX them 4) than males treated with placebo. Females did not experience more exual dysfunction on Cymbalta than on placebo as measured by ASEX total score. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that there is no evidence that its effects differ from other antidepressants. Physicians should routinely inquire about possible sexual side effects. See Table 5 in full P1 for specific ASEX results. **Urinary Hesitation**—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related. **Labbratory Changes**—Cymbalta treatment, for up to 9 weeks in MDD, 9-10 weeks in GAD, or 13 weeks in DPN placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analyses in Cymbalta-Terated aptaints when compared with placebo-created aptaints (see PPECAUTIONS). *Yital Sign Changes***—

in Cymbalta-treated patients when compared with placebo-treated patients (see PRECAUTIONS). Vital Stign Changes— In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure, averaging up to 2 mm Hg. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure (see PRECAUTIONS). Duloxetine treatment, for up to 13 weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3 beats per minute. Weight Changes—In placebo-controlled clinical trials, in heart rate compared to placebo of up to \$ beats per minute. Weight Changes—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13 weeks experienced a mean weight loss. Approximately 0.2 kg in placebo-treated patients and placebo-treated patients in clinical trials lasting up to 13 weeks. No clinically significant form dulovetine-treated patients and placebo-treated patients in clinical trials lasting up to 13 weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg BID, no prolongation of the corrected QT interval was observed. Postmarketing Spontaneous Reports—Adverse events reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, rash, Stevens-Johnson Syndrome, supraventricular arrhythmia, trismus, and urticaria.

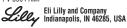
DRUG ABUSE AND DEPENDENCE: Controlled Substance Class—Duloxetine is not a controlled substance. Physical and Psychological Dependence—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats. While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed, consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE: There is limited clinical experience with Cymbalta overdose in humans. In clinical trials, cases of acute ingestions up to 3000 mg, alone or in combination with other drugs, were reported with none being tatal. However, in postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but positional religious perfective, fact outcomes have been reported to acute overlooses, printally with mixed overlooses, also with duloxetine only, at doses as low as approximately 1000 mg. Signs and symptoms of overdose (mostly with mixed drugs) included serotonin syndrome, somnolence, vomiting, and seizures. **Management of **Overdose**—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

Literature revised June 28, 2007

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Minority Research Training in Psychiatry

Through its National Institute of Mental Health-funded Program for Minority Research Training in Psychiatry (PMRTP), the American Psychiatric Institute for Research and Education (APIRE) is seeking to increase the number of minority psychiatrists going into psychiatric research.

The program provides medical students and psychiatric residents with funding for stipends, travel expenses, and tuition for an elective or summer experience in a research environment. Stipends are also available for one- or two-year post-residency fellowships for minority psychiatrists. Deadlines for applications are December 1 for residents seeking a year or more of training and for post-residency fellows; or three months before training is to begin for medical students. Summer medical students who will start their training by June 30 should submit their applications by April 1.

Training takes place at research-oriented departments of psychiatry in major U.S. medical schools and other appropriate sites nationwide. An individual at the site (the research "mentor") oversees the research training experience.

The PMRTP is administered by the American Psychiatric Institute for Research and Education (APIRE). The director of the program is Darrel A. Regier, M.D., M.P.H.; the project manager is Ernesto A. Guerra. An advisory committee of senior researchers and minority psychiatrists developed guidelines for applicants and criteria for selection. The members of this committee evaluate and select trainees.

For more information,
Call the toll-free number for the PMRTP
1-800-852-1390 or 703-907-8622
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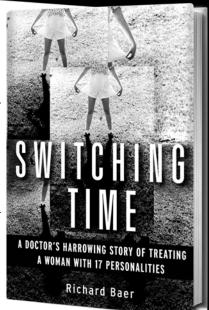
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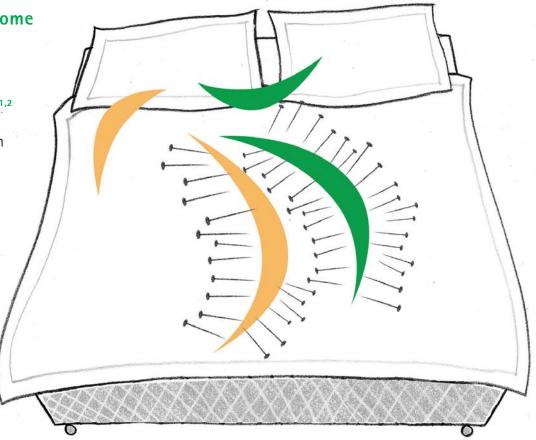
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Are your patients' restless legs to

Restless Legs Syndrome (RLS) is a common, underdiagnosed condition affecting a range of patients.^{1,2}

- Approximately 12 million Americans suffer from moderate to severe primary RLS^{1,3,4}
- A differential diagnosis can help rule out other health conditions that can cause problems with sleeping, including insomnia/sleep disorders, depression, or RLS¹



These essential criteria can help confirm RLS^{5,6}

- **Urge to move legs**—usually accompanied by uncomfortable leg sensations
- Symptoms begin or worsen during rest such as when lying or sitting
- Symptoms are partially or totally relieved by movement
- 4 Symptoms are worse in the evening or night

The only FDA-approved medications for the treatment of RLS are within the dopamine agonist (DA) class

blame for their sleepless nights?

Restless Legs Syndrome...Simplified

MIRAPEX offers effective, long-term relief from the symptoms of moderate to severe primary RLS⁷

- Well-established safety and tolerability profile
- No predicted P450 interactions
- Not a controlled substance
- Convenient dosing and titration
 - 75% of patients on the 0.25 mg dose of MIRAPEX responded to therapy*
 - MIRAPEX Starter Kit offers simple single-step titration[†]

IMPORTANT SAFETY INFORMATION ABOUT MIRAPEX: Patients have reported falling asleep without perceived warning signs during activities of daily living, including operation of a motor vehicle. Hallucinations and postural (orthostatic) hypotension may occur. The most commonly reported adverse events in RLS clinical trials for MIRAPEX vs placebo were nausea (16% vs 5%), headache (16% vs 15%), fatique (9% vs 7%), and somnolence (6% vs 3%).

Patients and caregivers should be informed that impulse control disorders/compulsive behaviors may occur while taking medicines, including pramipexole, to treat Parkinson's disease and RLS.

Please see accompanying Brief Summary of Prescribing Information.

Responders defined as patients with symptoms rated as "much improved" or "very much improved," as measured on the CGI-I.

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^{*}Results of a 12-week, placebo-controlled, randomized, double-blind, fixed-dose-treatment trial to assess the efficacy and safety of MIRAPEX vs placebo in the treatment of moderate to severe primary RLS.

[†]Provides samples of the first 2 dosage strengths. Additional titration steps may be needed to achieve symptom relief.

Brief Summary of Prescribing Information

Mirapex® (pramipexole dihydrochloride) 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 1.5 mg tablets

INDICATIONS AND USAGE

Parkinson's Disease: MIRAPEX tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's

Restless Legs Syndrome: MIRAPEX tablets are indicated for the treatment of moderate-to-severe primary Restless Legs

CONTRAINDICATIONS: MIRAPEX tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its

WARNINGS: Falling Asleep During Activities of Daily Living
Patients treated with Mirapex® (pramipexole dihydrochloride) have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Although many of these patients reported somnolence while on MIRAPEX tablets, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these ex-reported as late as one year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving MIRAPEX tablets at doses above 1.5 mg/day (0.5 mg TID) for Parkinson's disease. In controlled clinical trials in RLS, patients treated with MIRAPEX tablets at doses of 0.25-0.75 mg once a day, the incidence of somnolence was 6% compared to an incidence of 3% for placebo-treated patients (see ADVERSE EVENTS). Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge

drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with MIRAPEX tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with MIRAPEX tablets such as concomitant sedating medications, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (e.g., cimetidine – see PRECAUTIONS, Drug Interactions). If a patient develops significant daytime sleepiness of perisodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), MIRAPEX tablets should ordinarily be discontinued. If a decision is made to continue MIRAPEX tablets, patients should be advised to not drive and to avoid other potentially dangerous activities. While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Symptomatic Hypotension: Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, both Parkinson's disease patients and RLS patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk (see PRECAUTIONS, Information for Patients).

In clinical trials of pramipexole, however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to Miragex* (pramipsexed dihydrochloride) tablets than among those assigned to placebo. This result, especially with the higher doses used in Parkinson's disease, is clearly unexpected in light of the previous experience with the risks of dopamine agonist therapy.

While this finding could reflect a unique property of pramipsexole, it might also be explained by the conditions of the study and the nature of the population enrolled in the clinical trials. Patients were very carefully titrated, and patients with active cardiovascular disease or significant orthostatic hypotension at baseline were excluded. Also, clinical trials in patients with RLS did not incorporate orthostatic challenges with intensive blood pressure monitoring done in close temporal proximity to dosing.

Hallucinations: In the three double-blind, placebo-controlled trials in early Parkinson's disease, hallucinations were observed in 9% (35 of 388) of patients receiving MIRAPEX tablets, compared with 2.6% (6 of 235) of patients receiving placebo. In the four double-blind, placebo-controlled trials in advanced Parkinson's disease, where patients received MIRAPEX tablets and concomitant levedopa, hallucinations were observed in 16.5% (43 of 260) or patients receiving MIRAPEX tablets compared with 3.8% (10 of 264) of patients receiving placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 3.1% of the early Parkinson's disease patients and 2.7% of the advanced Parkinson's disease patients compared with about 0.4% of placebo patients in both populations.

Age appears to increase the risk of hallucinations attributable to pramipexole. In the early Parkinson's disease patients, the risk of hallucinations was 1.9 times greater than placebo in patients younger than 65 years and 6.8 times greater than placebo in patients older than 65 years. In the advanced Parkinson's disease patients, the risk of hallucinations was 3.5 times greater than

placebo in patients younger than 65 years and 5.2 times greater than placebo in patients older than 65 years.

In the RLS clinical program, one pramipexole-treated patient (of 889) reported hallucinations; this patient discontinued treatment and the symptoms resolved.

PRECAUTIONS

**Rhabdomyolysis: A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with MIRAPEX tablets. The patient was hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the medication. Renal: Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing Mirapex* (pramipexole dihydrochloride) tablets to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION in full Prescribing Information). Dyskinesia: MIRAPEX tablets may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia. Decreasing the dose of levodopa may ameliorate this side effect levocopa and may cause or exacercate preexisting dyskinesia. Decreasing the close of revocopa may ameliorate this sole effects of Rethial Pathology in Albino Rats: Pathologic changes (dependention and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study. While retinal degeneration was not diagnosed in pigmented rats treated for 2 years, a thinning in the outer nuclear layer of the retina was slightly greater in rats given drug compared with controls. Evaluation of the retinas of albino mice, monkeys, and minipigs did not reveal similar changes. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved (see ANIMAL TOXICOLOGY).

Exerts Reported with Doparminergic Therapy. Although the events enumerated below may not have been reported in association with the use of pramipexole in its development program, they are associated with the use of other doparminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopamineroic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date. Withdrawal-Emergent Hyperpyrexia and Confusion: Although not reported with pramipseous in the clinical development program, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy. Fibrotic Complications: Although not reported with pramipexole in the clinical development program, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening, pericarditis, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot derived dopamine agonists can cause them is unknown.

A small number of reports have been received of possible fibrotic complications, including peritoneal fibrosis, pleural fibrosis, and pulmonary fibrosis in the post-marketing experience for Mirapex^e (pramipexole dihydrochloride) tablets. While the evidence is not sufficient to establish a causal relationship between MIRAPEX tablets and these fibrotic complications, a contribution of MIRAPEX tablets cannot be completely ruled out in rare cases. *Melanoma*: Some epidemiologic studies have shown that patients with Parkinson's disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, was unclear. MIRAPEX tablets are one of the dopamine agonists used to treat Parkinson's disease. Although MIRAPEX tablets have not been associated with an increased risk of melanoma specifically, its potential role as a risk factor has not been systematically studied. Patients using MIRAPEX tablets for any indication should be made aware of these results and should undergo periodic dermatologic screening.

Impulse Control/Compulsive Behaviors: Cases of pathological gambling, hypersexuality, and compulsive eating (including binge eating) have been reported in patients treated with dopamine agonist therapy, including pramipexole therapy. As described in the literature, such behaviors are generally reversible upon dose reduction or treatment discontinuation.

Rebound and Augmentation in RLS: Reports in the literature indicate treatment of RLS with dopaminergic medications can

result in a shifting of symptoms to the early morning hours, referred to as rebound. Rebound was not reported in the clinical trials of MIRAPEX tablets but the trials were generally not of sufficient duration to capture this phenomenon. Augmentation has also been described during therapy for RLS. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. In a controlled trial of MIRAPEX tablets for RLIS, approximately 20% of both the Miraper. and placebo-treated patients reported at least a 2-hour earlier onset of symptoms during the day by the end of 3 months of treatment. The frequency and severity of augmentation and/or rebound after longer-term use of MIRAPEX tablets and the appropriate management of these events have not been adequately evaluated in controlled

Information for Patients (also see Patient Package Insert): Patients should be instructed to take MIRAPEX tablets only as

Patients should be alerted to the potential sedating effects associated with MIRAPEX tablets, including somnolence and the Pratients should be alreted to the potential sedaning effects associated with MilkPPCX tablets, including somnolence and repossibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with Mirapex* (pramipexole dihydrochloride) tablets to gauge whether or not it affects their method and/or motor performance adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Because of possible

dditive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with MIRAPEX tablets and when taking concomitant medications that increase plasma levels of pramipexole (e.g., cimetidine)

Patients should be informed that hallucinations can occur and that the elderly are at a higher risk than younger patients with

Parkinson's disease. In clinical trials, patients with RLS treated with pramipexule rarely reported hallucinations.

Patients and caregivers should be informed that impulse control disorders/compulsive behaviors may occur while taking medicines to treat Parkinson's disease or RLS, including MIRAPEX tablets. These include pathological gambling, hypersexuality and compulsive eating (including binge eating). If such behaviors are observed with MIRAPEX tablets, dose reduction or treatment discontinuation should be considered.

Patients may develop postural (orthostatic) hypotension, with or without symptoms such as dizziness, nausea, fainting or blackouts, and sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with MIRAPEX tablets.

Because the teratogenic potential of pramipexole has not been completely established in laboratory animals, and because experience in humans is limited, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, Pregnancy).

Because of the possibility that pramipexole may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

If patients develop nausea, they should be advised that taking MIRAPEX tablets with food may reduce the occurrence of

Taboratory Tests: During the development of MIRAPEX tablets, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his or her care.

Drug Interactions: Carbidopa/levodopa: Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (N=10), Pramipexole did not alter the extent of absorption (AUC) or the elimination of carbiologo/levodopa, although it caused an increase in levodopa C_{ms} by about 40% and a decrease in T_{ms} from 2.5 to 0.5 hours. Selegiline: In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics of pramipexole. Amantadine: Population pharmacokinetic analyses suggest that amantadine may slightly decrease the oral clearance of pramipexole. Printinguistics - Operation plant microbines and pages suggest of an alternation may spirit decrease the oral clearance of pramipexole. Circletine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (N=12). Probeneoid: Probeneoid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics (N=12). Other drugs eliminated via renal secretion: Population pharmacokinetic analysis suggests that coadministration of drugs that are secreted by the cationic transport system (e.g., cimetidine, ranitidine, dilitiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of pramipexole by about 20%, while those secreted by the anionic transport system (e.g., cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the oral clearance of pramipsoule. CVP interactions: Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipsoule elimination because pramipsoule of son dapprecably metabolized by these enzymes in two or in vitro. Permipsoule does not inhibit CVP enzymes CVP142, CVP2C9, CVP2C19, CVP2C19, and CVP3A4. Inhibition of CVP2D6 was observed with an apparent Ki of 30 µM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the clinical dose of 4.5 mg/day (1.5 mg TID). Departine antagonists: Since pramipexole is a departine agonist, it is possible that departine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of Mirapex[®] (pramipexole dihydrochloride) tablets.

Drug/Laboratory Test Interactions: There are no known interactions between MIRAPEX tablets and laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to Chbb:NMRI mice at doses of 0.3, 2, and 10 mg/kg/day [0,3, 2,2, and 11 times the Maximum Recommended Human Dose (MRHD) (MRHD of 1,5 mg TID on a m basis], Pramipevole was administered in the diet to Wistar rats at 0.3, 2, and 8 mg/kg/day (plasma AUCs were 0.3, 2.5, and 12.5 times the AUC in humans at the MRHD). No significant increases in tumors occurred in either species.

Pramipexole was not mutagenic or clastogenic in a battery of assays, including the in vitro Ames assay. V79 gene mutation assay for HGPRT mutants, chromosomal aberration assay in Chinese hamster ovary cells, and in vivo mouse micronucleus assay, In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day (5 times the MRHD on a mg/m² basis), prolonged estrus cycles and inhibited implantation. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for

inhibited implantation. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.

Pregnancy: Teratogenic Effect: Pregnancy Category C: When pramipoxole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/dgy (5 times the MRHD on a mg/m² basis). Administration of 1.5 mg/kg/dgy (6 pramipoxole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high indicience of total resorption of embryos. The plasma AUC in rats at this dose was 4 times the AUC in humans at the MRHD. These findings are thought to be due to the prolactin-lowering effect of pramipoxole, since prolactin is necessary for implantation and intenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of pramipoxole could not be adequately evaluated. There was no evidence of adverse effects or embryos, the development following administration of up to 10 mg/kg/dgy to pregnant rabbits during organogenesis (plasma AUC was 71 times that in humans at the MRHD). Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/dgy (approximately evaluatent). The MRHD of the MRHD of the mg/m² basis or orester during the latter part of pregnancy and throughout lactation.

equivalent to the MRHD on a mg/m² basis) or greater during the latter part of pregnancy and throughout lactation.

There are no studies of pramipexole in human pregnancy. Because animal reproduction studies are not always predictive of human response, pramipexole should be used during pregnancy only if the potential benefit outweighs the potential risk to the

Nursing Mothers: A single-dose, radio-labeled study showed that drug-related materials were excreted into the breast milk of lactating rats. Concentrations of radioactivity in milk were three to six times higher than concentrations in plasma at equivalent time points.

Other studies have shown that pramipexole treatment resulted in an inhibition of prolactin secretion in humans and rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pramipexole, a decision should be made as to whether to discontinue

nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of Mirapex[®] (pramipexole dihydrochloride) tablets in pediatric patients has not been

Geriatric Use: Pramipexole total oral clearance was approximately 30% lower in subjects older than 65 years compared with Genature Use: Pramiposole total oral clearance was approximately 30% lower in subjects older trian to syears compared with younger subjects, because of a decline in pramiposole renal clearance due to an aque-related reduction in renaturoin. This resulted in an increase in elimination half-life from approximately 8.5 hours to 12 hours. In clinical studies with Parkinson's disease patients, 38.7% of patients were older than 65 years. There were no apparent differences in efficacy or safety between older and younger patients, except that the relative risk of hallucination associated with the use of MIRAPSt tablets was increased in the elderly, in clinical studies with RLS patients, 22% of patients were at least 65 years old. There were no apparent differences in efficacy or safety between older and younger patients.

ADVERSE EVENTS

Parkinson's Disease: During the premarketing development of pramipexole, patients with either early or advanced Parkinson's disease were enrolled in clinical trials. Apart from the severity and duration of their disease, the two populations differed in their use of concomitant levodopa therapy. Patients with early disease did not receive concomitant levodopa therapy during treatment with pramipevole; those with advanced Parkinson's disease all received concomitant levodopa treatment. Because these two populations may have differential risks for various adverse events, this section will, in general, present adverse-event data for these two populations separately.

Because the controlled trials performed during premarketing development all used a titration design, with a resultant confounding of time and dose, it was impossible to adequately evaluate the effects of dose on the incidence of adverse events.

Early Parkinson's Disease: In the three double-blind, placebo-controlled trials of patients with early Parkinson's disease, the most

commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX tablets were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations.

Approximately 12% of 388 patients with early Parkinson's disease and treated with MIRAPEX tablets who participated in the

double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 11% of 235 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [3.1% on MIRAPEX tablets vs 0.4% on placebo]; dizziness [2.1% on MIRAPEX tablets vs 1% on placebo]; extrapyramidal syndrome [1.6% on MIRAPEX tablets vs 6.4% on placeboj; headache and confusion (1.3% and 1.0%, respectively, on Mirapex® (pramipexole dihydrochloride) tablets vs 0% on placeboj); headache and confusion (1.3% and 1.0%, respectively, on Mirapex® (pramipexole dihydrochloride) tablets vs 0% on placeboj); and gastrointestinal system (nausea (2.1% on MIRAPEX tablets vs 0.4% on placeboj).

**Adverse-event Incidence in Controlled Clinical Studies in Early Parkinson's Disease: This section lists treatment-emergent

adverse events that occurred in the double-blind, placebo-controlled studies in early Parkinson's disease that were reported by 1% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group. In these studies, patients did not receive concomitant levodopa. Adverse events were usually mild or moderate in intensity.

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 that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative

contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=388) vs placeto (N=38), respectively. Body as a whole: astherial (14% vs 12%), general edema (5% vs 3%), malaise (2% vs 1%), reaction unevaluable (2% vs 1%), fiver (1% vs 0%). Digestive system: nausea (28% vs 18%), constipation (14% vs 6%), anorexia (4% vs 2%), dysphagia (2% vs 0%), Metabolic and nutritional system: peripheral edema (5% vs 4%), decreased weight (2% vs 0%), formous system: dizziness (25% vs 24%), somnolence (22% vs 9%), insomnia (17% vs 12%), hallucinations (9% vs 3%), confusion (4% vs 1%), descreased weight (2% vs 0%), decreased libidous (2% vs 0%), triple (3% vs 0%), decreased libidous (2% vs 0%), triple (3% vs 0%), decreased libidous (3% vs 1%), descreased libidous (3% vs 1%), decreased libidous (3% vs 1%), descreased libidous (3% vs 1%), decreased libidous (3% vs 1%), descreased libidous (3% vs 1%), decreased libidous (3% vs 1%), descreased libid (1% vs 0%), myodonus (1% vs 0%). Special senses: vision abnormalities (3% vs 0%), Urogenital system: impotence (2% vs 1%), Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with early Parkinson's disease and treated with Mirapex® (pramipexole dihydrochloride) tablets but reported equally or more frequently in the placebo group were infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hypertonia, depression, abdominal pain, anxiety, dyspepsia, flatulence, plant, activity, as young, because injuries in hybridina depleasant, advisity, dyspepsal, natural diarrhea, rash, ataxia, dry mouth, extrapyramidal syndrome, leg cramps, twitching, pharyngitis, sunisitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, tooth disease, dyspnea, increased cough, gait abnormalities, urinary frequency, vomitting, allergic reaction, hypertension, pruritus, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accommodation abnormalities, tinnitus, diplopia, and taste perversions.

In a fixed-dose study in early Parkinson's disease, occurrence of the following events increased in frequency as the dose increased over the range from 1.5 mg/day to 6 mg/day, postural hypotension, nausea, constipation, somnolence, and amnesia. The frequency of these events was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg/day. The incidence of somnolence with pramipexole at a dose of 1.5 mg/day was comparable to that reported for placebo.

Advanced Parkinson's Disease in the four double-blind, placebo-controlled trials of patients with advanced Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX tablets and concomitant levodopa were postural (orthostatic) hypotension, dyskinesia, extrapyramidal syndrome,

insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, galt abnormality, hypertonia, dry mouth, amnesia, and urinary frequency. Approximately 12% of 260 patients with advanced Parkinson's disease who received Mirapex® (pramipexole dihydrochloride) tablets and concomitant levodopa in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 16% of 264 patients who received placebo and concomitant levodopa. The events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [2.7% on MIRAPEX tablets vs 0.4% on placebo]; dyskinesia [1.9% on MIRAPEX tablets vs 0.8% on placebo]; extrapyramidal syndrome [1.5% on MIRAPEX tablets vs 4.9% on placebo]; dizziness [1.2% on MIRAPEX tablets vs 1.5% on placebol; confusion [1.2% on MIRAPEX tablets vs 2.3% on placebol); and cardiovascular system (postural [orthostatic] hypotension [2.3% on MIRAPEX tablets vs 1.1% on placebol).

**Adverse-event Incidence in Controlled Clinical Studies in Advanced Parkinson's Disease: This section lists treatment-

emergent adverse events that occurred in the double-blind, placebo-controlled studies in advanced Parkinson's disease that were reported by 1% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group In these studies, MIRAPEX tablets or placebo was administered to patients who were also receiving concomitant levodopa Adverse events were usually mild or moderate in intensity.

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 that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments,

uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied. Treatment-mergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=260) vs placebo (N=264), respectively. Body as a whote: accidental injury (17% vs 15%), asthenia (10% vs 8%), general ederma (4% vs 3%), chest pain (3% vs 2%), malaise (3% vs 2%). Cardiovascular system: postural hypotension (53% vs 48%). Digestive system: constipation (10% vs 9%), or mouth (7% vs 3%), Metabotic and nutritional system: peripheral ederma (2% vs 18%), increased creatine K (1% vs 05%), Musculoskeletal system: arthritis (3% vs 18%), burdeling (2% vs 05%), bursitis (2% vs 05%), myasthenia (1% vs 05%). Orealme Pr (17 % to 79. millschuldsreiteral system: administ (57 % to 19.), witching (27 % to 20%), child sing (27 % to 27%), displayed (47 % to 31%), extrapriamidal syndrome (28% to 25%), insommia (27% to 27%), child syndrome (28% to 25%), insommia (27% to 27%), child syndrome (28% to 28%), child syndrom

thinks y lack infloating 14 is 3 by, with a size of the study or at disconfinuation; thus, patients may be included in more than one category.

Other events reported by 1% or more of patients with advanced Parkinson's disease and treated with Mirapex® (pramipexole dilhydrochloride) tablets but reported equally or more frequently in the placebo group were nausea, pain, infection, headache, depression, fremor, hypokinesia, anorexia, back pain, dyspepsia, flatulence, ataxia, flu syndrome, sinusitis, diarrhea, myalgia, abdominal pain, anxiety, rash, paresthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hypesthesia, neck pain, syncope, arthralgia, dysphagia, palpitations, pharynoitis, vertigo, leg cramps, conjunctivitis, and lacrimation disorders.

Restless Legs Syndrome: MIRAPEX tablets for treatment of RLS have been evaluated for safety in 889 patients, including 427 treated for over six months and 75 for over one year.

The overall safety assessment focuses on the results of three double-blind, placebo-controlled trials, in which 575 patients with RLS were treated with MIRAPEX tablets for up to 12 weeks. The most commonly observed adverse events with MIRAPEX tablets in the treatment of RLS (observed in >5% of pramipexole-treated patients and at a rate at least twice that observed in placebotreated patients) were nausea and somnolence. Occurrences of nausea and somnolence in clinical trials were generally mild and

Approximately 7% of 575 patients treated with MIRAPEX tablets during the double-blind periods of three placebo-controlled trials discontinued treatment due to adverse events compared to 5% of 223 patients who received placebo. The adverse event most commonly causing discontinuation of treatment was nausea (1%).

This section lists treatment-emergent events that occurred in three double-blind, placebo-controlled studies in RLS patients that were reported by 2% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo

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 that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse-event incidence rate in the population studied.

Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=575) vs

placebo (N=223), respectively. Gastrointestinal disorders: nausea (16% vs 5%), constipation (4% vs 1%), diarrhea (3% vs 1%), dry mouth (3% vs 1%). General disorders and administration site conditions: fatigue (9% vs 7%). Infections and infestations: influenza (3% vs 1%). Nervous system disorders: headache (16% vs 15%), somnolence (6% vs 3%). Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more

This section summarizes data for adverse events that appeared to be dose related in the 12-week fixed dose study. Dose related adverse events in a 12-week, double-blind, placebo-controlled, fixed dose study in Restless Legs Syndrome (occurring in 5% or more of all patients in the treatment phase) are listed by body system in order of decreasing incidence for MIRAPEX (0.25 mg [N=88]; 0.5 mg [N=80]; 0.75 mg [N=90]) vs placebo (n=86), respectively. *Gastrointestinal disorders*: nausea (11%; 19%; 27% vs 5%), diarrhea (3%; 1%; 7% vs 0%), dyspepsia (3%; 1%; 4% vs 7%). *Infections and infestations*: influenza (1%; 4%; 4%; 4%) vs 7%). 7% vs 1%). General disorders and administration site conditions: fatigue (3%; 5%; 7% vs 5%). Psychiatric disorders: insomnia (9%, 9%, 13% vs 9%), abnormal dreams (2%; 1%; 8% vs 2%). Respiratory, thoracic and mediastinal disorders: nasal congestion (0%; 3%; 6% vs 1%). Musculoskeletal and connective tissue disorders: pain in extremity (3%; 3%; 7% vs

Other events reported by 2% or more of RLS patients treated with Mirapex[®] (pramipexole dihydrochloride) tablets but equally or more frequently in the placebo group, were: vomiting, nasopharyngitis, back pain, pain in extremity, dizziness, and insomnia. General

Adverse Events: Relationship to Age, Gender, and Race: Among the treatment-emergent adverse events in patients treated with MIRAPEX tablets, hallucination appeared to exhibit a positive relationship to age in patients with Parkinson's disease. Although no gender-related differences were observed in Parkinson's disease patients, nausea and fatigue, both generally transient, were more frequently reported by female than male RLS patients, Less than 4% of patients enrolled were non-Caucasian, therefore, an evaluation

of adverse events related to race is not possible.

Other Adverse Events Observed During Phase 2 and 3 Clinical Trials: MIRAPEX tablets have been administered to 1620 Parkinson's disease patients and to 889 RLS patients in Phase 2 and 3 clinical trials. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing; similar types of events were grouped into a smaller number of standardized categories using MedDRA dictionary terminology. These categories are used in the listing below. Adverse events which are not listed above but occurred on at least two occasions (one occasion if the event was serious) in the 2509 individuals exposed to MIRAPEX tablets are listed below. The reported events below are included without regard to determination of a causal relationship to MIRAPEX tablets.

Blood and lymphatic system disorders: anemia, iron deficiency anemia, leukocytosis, leukopenia, lymphadenitis, lymphadenopathy,

Blood and Immphatic system disorders: anemia, iron deficiency anemia, leukocytosis, leukopenia, Immphatedisis, Immphatedenopathy, iromboorphatemia, thromboorphatemia, thromboorphatemis aphthous stomatitis, ascites, chellitis, colitis, colitis, ulcerative, duodenal ulcer, duodenal ulcer hemorrhage, enteritis, eructation, fecal incontinence, gastric ulcer, gastric ulcer hemorrhage, gastritis, gastrointestinal hemorrhage, gastroesophageal reflux disease, gingivitis, haematemesis, haematochezia, hemorrhoids, hiatus hernia, hyperchlorhydria, ileus, inguinal hernia, intestinal obstruction,

irritable bowel syndrome, esophageal spasm, esophageal stenosis, esophagitis, pancreatitis, periodontitis, rectal hemorrhage, reflux esophagitis, tongue edema, tongue ulceration, toothache, umbilical hemia. General disorders: chest discomfort, chills, death, drug withdrawal syndrome, face edema, feeling cold, feeling into feeling littery, gait disturbance, impaired healing, influenza-like illness, irritability, localized edema, edema, pitting edema, thirst. Hepatobiliary disorders: biliary colic, cholecystitis, cholecystitis chronic, cholelithiasis. Immune system disorders: drug hypersensitivity. Infections and infestations: abscess, acute tonsillitis, appendicitis, bronchiolitis, bronchitis, bronchopneumonia, cellulitis, cystitis, dental caries, diverticulitis, ear infection, eve infection, folliculitis, funga infection, fruncle, gangrene, gastroenterinis, gingiyal infection, herpes simplex, herpes zoster, hordeolum, intenerebral discitis, laryngitis, lobar pneumonia, nail infection, onychomycosis, oral candidiasis, orchitis, osteomyelitis, otitis externa, otitis media, paronychia, pyelonephritis, pyoderma, sepsis, skin infection, tonsilitis, tooth abscess, tooth infection, upper respiratory tract infection, peroriginal, preconsings, procuring, especial, estimation, tollarials, political, and infection, infection, procuring and procedural complications: urethritis, vaginal candidiasis, vaginal infection, viral infection, wound infection. Injury, poisoning and procedural complications: accidental falls, drug toxicity epicondylitis, road traffic accident, sunburn, tendon rupture. Metabolism and nutrition disorders: cachexia, decreased appetite, dehydration, diabetes mellitus, fluid retention, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hyperunicemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, hypovitaminosis, increased appetite, metabolic alkalosis. Musculoskeletal and connective tissue disorders: bone pain, fasciitis, flank pain, intervertebral disc disorder, intervertebral disc protrusion, joint effusion, joint stiffness, joint swelling, monarthritis, muscle rigidity, muscle spasms, musculoskeletal stiffness, myopathy, myositis, nuchal rigidity, osteoarthritis, osteonecrosis, osteoporosis, polymyalgia, rheumatoid arthritis, shoulder sumness, myopatmy, myosins, nucrial rigiority, osteoarminis, osteoarcorsis, osteoporosis, polymylagila, meumatiou arminis, snoiuda pain, spinal osteoarthritis, tendonitis, tenosymvitis. Neoplasms benigin, malignant and unspecified: abdominial neoplasm, adenocarcinoma, adenoma benigin, basal cell carcinoma, bladder cancer, breast cancer, breast neoplasm, chronic lymphocytic leukemia, colon cancer, colorectal cancer, endometrial cancer, gallbladder cancer, gastric cancer, gastrointestinal neoplasm, hemangioma, hepatic neoplasm, hepatic neoplasm malignant, lipin and/or oral cavity cancer, lung neoplasm malignant, lung cancer metastatic, lymphoma, malignant melanoma, melanocytic naevus, metastases to lung, multiple myeloma, oral neoplasm benigin, neoplasm, neoplasm malignant, neoplasm prostate, neoplasm skin, neuroma, ovarian cancer, prostate cancer, prostatic adenoma, pseudo lymphoma, renal neoplasm, skin cancer, skin papilioma, squamous cell carcinoma, thyroid neoplasm, uterine leiomyoma. Nervous system disorders: ageusia, akinesia, anticholinergic syndrome, aphasia, balance disorder, brain edema, carotid artery occlusion, carpal tunnel syndrome, cerebral artery embolism, cerebral hemorrhage, cerebral infarction, cerebral ischemia, chorea, cognitive disorder, coma, convulsion, coordination abnormal, dementia, depressed level of consciousness, disturbance in attention, dizziness postural, dysarthia, dysgraphia, facial palsy, grand mal comulsion, hemiplegia, hyperaesthesia, hyperflexia, hyporeflexia, hypotonia, lethargy, loss of consciousness, memory impairment, migraine, muscle contractions involuntary, narcolepsy, neuralgia, neuropathy, nystagmus, parosmia, psychomotor hyperactivity, sciatica, sedation, sensory disturbance, sleep phase rhythm disturbance, seleep talking, stupor, syncope vasonagal, tension headache. Psychiatric disorders affect lability, aggression, agitation, bradyphrenia, bruxism, suicide, delirium, delusional disorder persecutory type, disorientation, dissociation, emotional distress, euphoric mood, hallucination auditory, hallucination visual, initial insomnia, libido increased, mania, middle insomnia, mood altered, nightmare, obsessive thoughts, obsessive-compulsive disorder, panic reaction, parasomnia, personality disorder, psychotic disorder, restlessness, sleep walking, suicidal ideation. Renal and urinary disorders: chromaturia, dysuria, glycosuria, hematuria, urgency, nephrolitism, peurogenic bladder, nocturia, oliquiria, polaliuria, renal artery tensois, renal colic, renal cyst, ernal fallure, renal impairment, urinary retention. Reproductive system and breast disorders: amenorrhea, breast pain, dysmenorrhea, epididymitis, gynaecomastia, menopausal symptoms, menorrhagia, metorrhagia, ovarian cyst, priapism, prostatti, sexual dyfunction, uterine hemorrhage, vaginal discharge, vaginal hemorrhage. Respiratory, thoracic and mediastinal disorders: apnea, aspiration, asthma, choking, chronic obstructive pulmonary disease, dry throat, dysphonia, dyspnea exertional, epistaxis, haemoptysis, hiccups, hyperventilation, increased bronchial secretion, laryngospan, nasal dryness, nasal polyse, obstructive airways disorder, pharyngolaryngeal pain, pleurisy, pneumoria aspiration, pneumothorax, postnasal drip, productive cough, pulmonary embolism, pulmonary edema, respiratory alkalosis, respiratory distress, respiratory failure, respiratory tract congestion, rhinitis allergic, rhinorrhea, Sinus congestion, sleep apnoea syndrome, sneezing, snoring, tachypnea, wheezing. Skin and subcutaneous tissue disorders: acne, alopecia, cold sweat, dermal cyst, dermatitis, dermatitis bullous, dermatitis contact, dry skin, ecchymosis, eczema, erythema, hyperkeratosis, livedo reticularis, night sweats, periorbital edema, petechiae, photosensitivity allergic reaction, psoriasis, purpura, rash erythematous, rash maculo-papular, rash papular, rosacea, seborrhea, seborrheic dermatitis, skin burning sensation, skin discoloration, skin exfoliation, skin hyperignentation, skin hypertrophy, skin irritation, skin nodule, skin odor abnormal, skin ulcer urticaria. Vascular disorders: aneurysm, angiopathy, arteriosclerosis, circulatory collapse, deep vein thrombosis, embolism, hematoma, hot flush, hypertensive crisis, lymphoedema, pallor, phlebitis, Raynaud's phenomenon, shock, thrombophlebitis, thrombosis, varicose

Falling Asleep During Activities of Daily Living: Patients treated with Mirapex[®] (pramipexole dihydrochloride) tablets have reported falling asleep while engaged in activities of daily living, including operation of a motor vehicle which sometimes resulted in accidents (see bolded WARNING).

In accidents (see order WANNING).

Post-Marketing Experience: In addition to the adverse events reported during clinical trials, the following adverse reactions have been identified during post-approval use of MIRAPEX tablets, primarily in Parkinson's disease patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to pramipscule tablets. Similar types of events were grouped into a smaller number of standardized categories using the MeDical dictionary, abortional features about many societies (footding fall) belegants faiting bellutions (all kinds). indictionary, abnormal behavior, abnormal dreams, accidents (including fail), blackouts, fatigue, hallucinations (all kinds), headache, hypotension (including postural hypotension), increased eating (including binge eating, compulsive eating, and hyperphagia), libido disorders (including increased and decreased libido, and hypersexuality), pathological gambling, syncope,

DRUG ABUSE AND DEPENDENCE

Pramipexole is not a controlled substance. Pramipexole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, in a rat model on cocaine self-administration, pramipexole had little or no

OVERDOSAGE

There is no clinical experience with massive overdosage. One patient, with a 10-year history of schizophrenia, took 11 mg/day of pramipevole for 2 days in a clinical trial to evaluate the effect of pramipevole in schizophrenic patients. No adverse events were reported related to the increased dose. Blood pressure remained stable although pulse rate increased to between 100 and 120 beats/minute. The patient withdrew from the study at the end of week 2 due to lack of efficacy.

There is no known antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdosage has not been assessed. Management of overdose may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring.

ANIMAL TOXICOLOGY

ANIMAL TOXICOLOGY
Retinal Pathology in Albino Rats: Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study with pramipexole. These findings were first observed during week 76 and were dose dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times the AUC in humans the received 1.5 mg TID). In a similar study of pigmented rats with 2 years' exposure to pramipexole at 2 or 8 mg/kg/day, retinal degeneration was not diagnosed. Animals given drug had thinning in the outer nuclear layer of the retina that was only slightly greater than that seen in control rats utilizing morphometry.

Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photoreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of degeneration and loss of photoreceptor cells occurred in alunion rats after 13 weeks of treatment with 25 mg/kg/day or pramipiexole (54 times the highest clinical dose on a mg/m² basis) and constant light (100 lux) but not in pignented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats is considered to be uniquely sensitive to the damaging effects of pramipexole and light. Smilar changes in the retina did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.3, 2.2 and 11 times the highest clinical dose on a mg/m² basis). Evaluation of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipiexole (0.4, 2.2, and 8.6 times the highest clinical dose on a mg/m² basis) for 12 months and miniping given 0.3, 1, or 5 mg/kg/day of pramipiexole for 13 weeks also detected no changes. The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally increased in waterbasic (a. disk chefficin) may be inpulsed.

The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (e.e., disk shedding) may be involved.

Fibro-osseous Proliferative Lesions in Mice: An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on anym² basis), Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is not known.

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Rx only





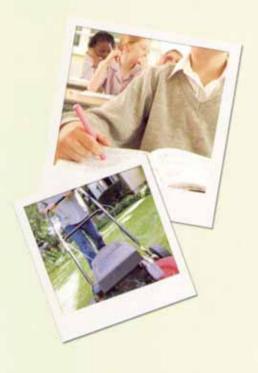


CONCERTA® CAN MAKE A DIFFERENCE



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.



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

ONCE-DAILY



Delivering results that matter

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!
- Improves academic performance and classroom behavior in children with ADHD²
- Significantly reduces ADHD symptoms and conflict with family members in adolescents with ADHD³

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.

CONOT-034
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Expires 6/98

CONCERTA® © (methylphenidate HCl) Extended-release Tablets

ARIEF SUMMARY: Please see full prescribing information. DESCRIPTION

is a central nervous system (CNS) stimulant, CONCERTAⁿ is available in four tid strengths. Each extended-release fablet for ence-a-day onal administration contains 18, 27, 36, or 54 mg of methylpheridate HD 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 appropriate these symptoms.

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

Glaucena: CONICETTA* is contraindicated in patients with glaucona.

Galacteria. SUNUEZHIA* is contrainstant on patients with pactions.

These CONCEPTA* is contrainational or patients with motor liss or with a family testory or diagnosis of Tourtte's sundrome (see ADVERSE REACTIONS).

Monoranine Oxidate left-billionic CONCERTA* is contrainated during trustment with monoranine oxidate (IAMC) reflectors, and also within a minimum of 14 days following discontinuation of a MACI-enhibitor (hypertensive cross may result) (see PRECAUTIONS. Drug Interactions) WARNINGS

WARNINGS
Series Carliovascular Events: Sudden Death and Pre-existing Structural Certise: Abnormalities or Other Serious Head Frodering
Children and Adolescents, Sudden death may been reported in association with CNS structural certise; solved reads may be reported in association with CNS structural certise; abnormalities or other serious head problems above carry as increased other serious head problems above carry as increased. risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac zbroomalities, cardiomyopathy, serious heart rhytim abnormalities, or other serious cardiac problems that may place them at increased valmenability

to the sympathonisms effects of a standard drug.

Adults: Soutien deaths, strike, and inyocardial infanction have been reported in adults taking strainant drugs is suited does for ADULE. 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, serous heart rhytern abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not

be treated with stimulant drugs.

pe treate versi am unimum coups. Hipertension and other Continuescular Conditions, Stimulant medications cause a modes increase in average blood pressure labout 2-4 mining) and average heart rate (about 3-6 open [use Adverse Reactions-Hypertension], and individuals may have larger increases. While the nean changes allow would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Cuction 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 impocantial effections, or verticate arrhythmia.

important effection, or writteness arrivations. Appeared seeds seed Stressert Medications Caldient, addresserbs, or authly who are being considered for treatment with stresserd medications, should have a careful featory including assessment for a brinly hattory of southern death or writtings are religious and the seasons for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who divelop symptoms such as exertional chest pain, unexplained syncope, or lither symptoms suggestive of cardioc disease during stimulant treatment should undergo a prompt cardioc evaluation.

Psychiatric Afverse Events: Pre-Existing Psychosis: Administration of stimulants may excertaite symptoms of behavior and thought disorder in patients with a pre-existing

Booke Rees: Particular care should be taken in using stimularts to heat ADHO in spaces with corrorfed byoter decoder festales of concern for possible induction of a mixed thanks greate in such patients. Prior to inflating treatment with a stimulant, patients with cornorfed depressive symptoms should be adequately screened to determine if they are at

real for begind decreter, such screening should include a detailed psychiatric history, including a territy fisitory of suicide, bipolar departer, and depression. Emergence, of Neep Psychotic or Marie, Syraptorys: Treatment emergent spectroic or marie syraptorys, e.g., fisikunomizins, debisional thinking, or maries are children and adolescents without a pilor history of psychotic riferess or maries can be caused by stimularies at usual doses. If such symptoms occurs consideration should be given to a possible causal role of the content of t stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple strict-term, placebo-controlled studies, such symptoms occurred in about 0.7% (4 publishs with events out of 3452 exposed to methylphenidate or amphilatmine for several news at usual lesses) of stimulant-breated patients compared to 0 in placebo-breated patients.

Aggression Aggressive behavior or hostility is often observed in children and advisouritis with ACHD, and has been reported in clinical triats and the postmarketing experience of some medications indicated for the historiest of ACHD. Although there is no systematic mixtories this stimulants cause aggressive behavior or hostility, patients beginning treatment for ACHD should be increased for the appearance of or womening of aggressive

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 treatment groups over 14 months, as well as in raturalistic pubgroups of month methylphenidate-hashed and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., frautment for 7 days per week throughout the year) have a temporary stowing as growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less provid in weight over 3 years), without evidence of growth rebound sharing this presid of development. Published data an inadequate to adventure whether chronic. use of amphetamines may cause samilar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stanularity, and patients who are not growing or gaining height or weight as expected may need

to tuse their treatment interrupted. Setures: There is some clinical evidence that stimularies may los in patients with prior history of sectures, in patients with prior EEG abnormalities in absence of sectures, and, very rarely, in patients without a history of sectures and no prior EEG evidence of telesces. In the presence of sectures, the drug should be decontinued.

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

eith stimulant triatment

Patential for Gastrointestinal Obstruction: Broason the CONCERTA[®] tablet is nondeformable and does not appropriately change in shape in the GI tract, CONCERTA® should not ordinarily be administrated to patients with presenting severa particularities inanceing (pathologic or al-regence, for example: escaphages motility discorders, small bowle inflammatary steams, whom guilt injudicies to adhesions or discorders trained time, past history of peritorities, cystics, fibrosis, chronic intestinal possociostection, or Median's (windown). There have been raise necrosis, ordered, resistant productions could be executed by an experimental production of the experiment of drugs in modelformable controlled-release formulations. Our to the controlled-release design of the state, CONCETTA' should only be used in patients who are able to swillow the table whose per PRECALTIONS introvation for Pretends.

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 best established.

CONCERTA® should be given cautiously to patients with a history of drug dependence or atroholism. Chronic absolve use can lead to marked tolerance and psychological depensuccessions, current, expense account size of markets transported and physicilogical department of whom of whying degrees of differential features. Frame specified personal conductive expensions in required during withstrans from abstract extense depression may occur. Whiteheast following charries throughouts used may currently extension frameworks as may come for the conductive of the c

PRECAUTIONS

agic Monitoring: Periodic CBC, differential, and plateter counts are advised during

processes transport control to the particular process of the particular process of the particular process of the particular process of the particular processes. The medication is contained within a monitorintable shall designed to release the drug at a controlled one. The table shall along with insolution consistency of the particular processes.

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: CONCERTAL should not be used in patients being treated (currently or within the proceeding 2 weeks) with MAD inhibitors (see CONTRANDICATIONS, Norosammir Oxidase inhibitors), Securise of possible increases in blood pressure, CONCERTAL should be circular innouncing, because or prosses reference is store presenter, consuctive factors and cardiovally with valappears aganta. Human pharmacologic states that exhount that methyloteristate may winkle the metabolism of coursains anticoaptizets, anticoavulants, leg, phenotostatizat, prenytion, primitioner, and some antidepressants (https://cis.cs.and.selective.selection) regulate antidepressants (https://cis.cs.and.selective.selection) provides antidepressants (https://cis.cs.and.selective.selection) provides antidepressants (https://cis.cs.and.selection) provides antidepressants (ht eported in concomitant use with doniders, although no causality for the combination has been stablished. The safety of using methylphenidate in combination with clonidine or other centrally active alpha-2 agonetis has not been systematically evaluated.

away surver a systems rear not cent systemistically extracted. Continuogenesis, Multispenesis, and hopoliment of Fertility; in a librime carcinogenicity study, carried out in 960,311 mice, methylpheriotale caused an increase in hepaticolistor administration and, as males only, as increase in hepaticolistora administration of a daily dote of approximately 60 may large the continuum recommended human dose of CONCERTA? on a mightig and mightir basis, respectively. Hepaticolistora is a institutely care modern multiplant further type. These was no increase in tool inalgorant human free. heads shrains. The chause state used is sensitive to the development of heads turnors, and the significance of these results to humans is unknown. Methylphenidate did not plause any econoses in turnors in a letterine consciopmently study cornical to 1534 sets. The highest done used was approximately 45 majkingtile, which is approximately 25 times and 5 times in maintain recommended human dose of CONCEPTA* on a migking and might? besin, respectively, bit in 24-week contraopments shady in the hadesprice recurse strain gibbs-1, which is sensitive to genotice contraopments thanky in the hadesprice recurse strain gibbs-1, which is sensitive to genotice contralingems, there was ne evidence of contraopmicity. Male and female mice were led detail containing the same concentration of methylphenidate as in the litterine contribution of methylphenidate as in the litterine contraction of the vivin Arms review multiple costs of the vivin microsis protons and toward multiple costs. Settle critiquial containers atic furthers. The mouse strain used is sensitive to the development of hepatic furners assay or the in vitro mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome abenutions were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Overy cells. Methylphenidate was regulite in vivo in males and females in the mouse bone marrow micronucleus assay. Methylphenidate did not impair lettify in male or female misc that were field diets containing the drug in an 15-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/stay, approximately 80-fold and 6-fold the highest recommended furnain date of CONCERTA² on a to besix or

registra and regim basis, respectively. Pregnancy: Tendogenic Effects: Physiciancy Category C: Methylpheridate has been shown to have testoporic effects in natios, when given in doses of 200 registrate, which is approximately 100 lines and 40 times the maximum recommended human dose on a registration. approximately 100 times and 40 times the insulativity in data revealed human dose on a rigidy and mightin basis, respectively. A regriduction study in data revealed no evidence of harm to the less as one dose of DONCERTA* on a rigidy and rigidity 15-bid and 3-bid the maximum recommended human dose of DONCERTA* on a rigidy and rigidity less, espectively. The approximate plasma exposure to methylphericities plast its main metabolite PPA in pregnant risks was 2 times that been in that in volunteers and patients with the maximum recommended dose of CONCERTA* based on the ALC. The safety of methylphericities have been recommended dose of CONCERTA* based on the ALC. The safety of methylphericities to use during human pregnant vierness. CONCERTA* about the last during pregnancy only if the potential benefit satisfies the potential risk to the fature.

Namina Methors: It is not known whether methyloherotate is excepted in hum drugs are excelled in framen milk, caution should be exercised if CONCERTA[®] is of to a nursing women.

Pediatric Use: The safety and efficacy of CONCERTA® in children under 6 years old have m effects of methylpheridate in children have not been well

ADVERSE REACTIONS

ANYTHIS TOUCH THE PROPERTY OF CONCERTENT INcluded exposures in a total of 2121 surficipants in climat trials (1767 patients, 224 houtiny abut subjects). These participants reserved CONCERTAN 18, 36, 54, and/or 72 mg/lay, Discovir, adolescents, and adults with ADHO were evaluated in thus controlled crinical studies, three open-laber clinical studies and two clinical studies are studies and two clinical studies are studies and two clinical studies and two clinical studies are studies and two clinical studies are studies are studies are during exposure were obtained primarily by general inquiry and inconded by clinical investiga-turs 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 standardised event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events. The stated tragencies of adverse events impresent the proportion of inducing all with experiences, at least once, a footbrent-energiest adverse event of the type fielded, An event vius considered Impatment emergent if it occurred for the first time or worsened while

recovering therapy reserving baseline evaluation.

Adverse Findings in Clinical Trials with CONCERTA*: Adverse Events Associated with fination of instructs in the 4-veek picobo controlled, parallel group that in chicken.

3) one CONCEHIA-frozand patient (0.9%, 1706), and one picobo-treated patient.

1/99; deconfinued the to an adverse event (satiness and increase in fics, respectively). (1.0% 199) disconfined the to an adverse event (subtress and increase in tion, respectively). In the 2-week placebol controlled phase of a trial in advisements (Study 4. In CONDERTA*) health patient, 10% 087) and 1 placebol-burstle patient (1.1% 199) disconfined that is an adverse event (increased model intuitibility, in the two oper-label, long-term substy this (Souties 5 and 6 one 24-month study in dishler augle 6 to 10 and one 5-month study in children augle 6 to 10 and one 5-month study in children augle 6 to 10 and one 5-month study in child, adolescent and adult patients freshed with CONDERTA*) 6.7% (101/1514) of patients disconfined due to adverse events. These events with an incidence of 3-0.5% included, morrorma (15-5%, hostolings) (15%), incidence and (15.7%), and anveyora (1.7%), and anveyora (1.7%).

point or 7%, and annowal (or 7%). That there's Energed Advence Events Amores CONCERTA** I braish 2 placets: Table 1 enumerates, for a 4-week placeto-controlled, parallel group that (Stady 3) in children with ADHO at CONCERTA** doses of 1% 36; or 54 mystads; the incidence of treatment-energent adverse events that the table incidence only those events that occurred in 1%, or more of patients freshed with CONCERTA** where the incidence in patients treated with CONCERTA** was greater than the incidence in placeto-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse everys in the course of usual medical practice where patient characteristics and other bactors differ from those which precised in the clinical trists. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigation. The olded figures, to do provide the prescribing physician with some basis for estimating the relative contributing 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

Body System	Preferred Term	CONCERTA® (n=106)	Placebo (n= 99) 10 %		
General	Hostuche	14%			
Digestive	Abdominal pain (stomachache) Vorsiting	7% 4%	1% 3%		
Nervous	(loss of appetite) Dizzness Insomria	4% 2% 4%	0% 0%		
Respiratory	Upper Respiratory Tract Infection Cough Increased Proxyrights	E% 4% 4%	5% 2% 3%		

Events, regardless of casuality, for which the incidence for patients histed with CONCERTA* was at least 1% and greater than the incidence among placebo-freated patients, incidence has been rounded to the nearest whole number.

Table 2 lots the incidence of treatment-intergent adverse events for a 2-week placeto-controlled trial (Study 4) in adolescents with ADHO at DONCERTA® doors of 18, 36, 54 or 72 mg/day.

Table 2 Incidence of Treatment-Emergent Events' in a 2-Week

Body System	Preferred Term	CONCERTA* (n=87)	Placebo (n= 90)		
General	Accidental injury Fever	6% 3%	3%		
Digestive	Hoadache Anoresia Diarrhea	9% 2% 2%	8% 0% 0%		
Nervous Respiratory	Voroting Insomise Phannotis	3% 5% 2%	0% 0%		
Urogenital	Rheits Dysmenorthea	3%	2%		

1: Events, regardless of causality, for which the incidence for putients treated with CONCERTA

was at least 2% and grader than the incidence among placebo-healted patients, incidence has been manded to the nearest whole number. Togg in a large-plant moderated study (in-452 of higher), the cumulative incidence of new order of tiss was 5% after 27 months of treatment with COMCERTA** In a second uncontrolled study.

or co. see 54 years 2 months or inserting with CVICATOR. In a second convisions stay, in-622 children, the currilyable moderace of new creat loss was 1% (\$652 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months. Hygeringsor: In the laboratory classroom clinical risks in children (Studies 1.5 and 2), both CONCERON* of and methydrenicidate foll increased resturp pulse by an average of 2-6 both and produced average increases of systalic and distillate blood pressure of roughly 1-4 months during the day, relative to placebo. In the placebo-controlled activisation that (Study 4), mean increases from baseline in resting public rate were observed with COMCERTAP and placebo at the end of the double-olled phase itS and 3 baselshinster, expectively. Mean increases from baseline in Blood pressure at the end of the obuble-blind phase for COMCERTAP and placebo-insated patients, were 0.7 and 0.7 mm Hig (systolic) and 2.6 and 1.4 mm Hig (diamblic). spectively, (see WARNINGS)

respectively, (one inversarials). Post-marketing Experience with CONCERTA** Post-marketing experiences with CONCERTA* associated revealed sportaneous reports of the following adverse events: difficulties in visual accommodition, blurred vision, athormal liver function first (e.g., transaminate elevation).

populations, arthylinia, Hucopera, and Frontocytopera.

Adverse Events with Other Methylphenidate HCI Products: Nervousness and Insomnia are the most common adverse reachors reported with other methylphemicate products. Other reactions include hypersensitivity (including skin raph, unicaria, heier, arthraigia, exfoliative dermatitis, erythema mutiflorme with histopathological findings of necrotizing sepolatis, and demonstrating registers in requirement were insequent output in restricting sections, and thromboorphomic purpositio arrowest, master, dictoriess, headacht, dysteriess, drowleress, blood pressure and pulse changes, both up and desert befrucardis, angins abdominal pairs weight base during purposing of thereopy. There have been true reports of flowerfels syndrome. Tools, psychosis has been reported, Although a definite causal relationship has not been established, the following have been reported in patients falling this drugs hapitic comis, related cause of certifical artistics and/or codesions, areming fallingered specification of a few instances of scale hard loss. Wery care reports of recording majoriest depressed mood, a few instances of scale hard loss. Wery care reports of recordingtic malignant spectrum (WAS) have been revisited and in more of these contents were consumers revision between the testing ways. have been received, and, in most of treat, patients were comparently receiving therapies associated with NMS. In a single report, a ten-year-old boy who had been taking methylphenidate for approximately 16 months experienced an NMS-Re event within 45 minutes of ingesting his first dose of ventationse. 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 tachycleriae may occur more frequently. rse reactions listed above may also occur

DRUG ABUSE AND DEPENDENCE

Controlled Solstance Class: CONCERTA*, like other methylphenidate products, is classified as a Schedule if controlled substance by kideral regulation.

Abuse, Dependence, and Talerance: See WARNINGS for boxed warning containing drug.

Sinns and Symptoms: Sizes and sumptoms of acute methylpheridate overdiscipe, resulting Signs are symptomic signs and symptoms of acute metrylphenolate composition, mission, principally from devisitinuation of the CNS and from excesse sympathonismistic effects, may include the following-contiling, aptation, formors, fryperefficial, muscle hyliching, comunicions (may be followed by coma), explicing, confusion, full schalarons, delirium, sweating, flushing. heutache, hyperpyresia, tachycardia, palpitations, cardiac arrhythmias, hypertension, and dryness of mucous membranes.

and dryriess of mucous membranes. Recommended Treatment: Treatment consists of appropriate supportive measures. The patient must be protected against self-visiny and against external stimuli that routil against overstimulation sinadly present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and secures if present as indicated, before performing gaster, usage, control applicant and systems in present and present the airway. Other ressures to debudy the gut include administration of activated charcost and a cathoric, intensive core must be provided to maintain adequate circulation and respectively exchange, external corting procedures may be required for hyperpy-reas. Efficacy of pertoned dialyses or extractory resil hemodalysis for CONCERTA? include feat not been established. The prolonged release of methysphemiotals from CONCERTA? should be considered when treating patients with previous.

se considered when this originates with oversions, or defending the possibility of multiple fing 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 ethylphenidate.

For more information call 1-856-440-7903 or shift www.concerta.net Manufactured by ALZA Corporation Mountain View CA 94043. Distributed and marketed by McNeil Pediatrics, Dission of McNeil-PPC, Inc., Fort Washington, PA 19034.



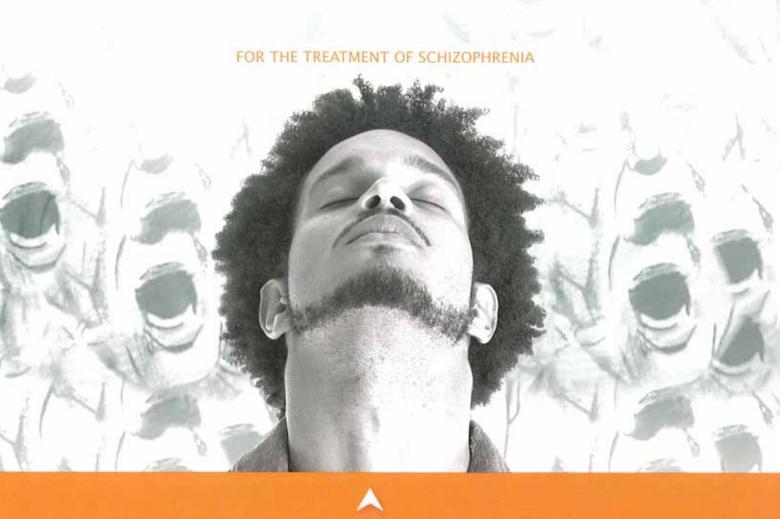
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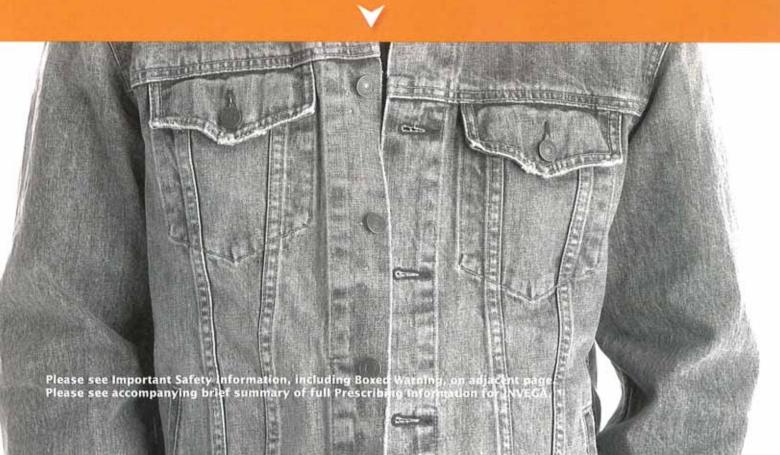
Edition: June 2006 10025803 PF

References: 1. McBurnett K. Cooper KM. Effectiveness of OROS[®] methylphenidati in children with or without comorbid oppositional deflant 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, Ontano, Canada. 2, Pelham WE, Ghapy EM. Burrows-Madiean L, et al. Once-a-day Concerta methylphenidate versus three daily methylpheridate in laboratory and natural settings. Pediatrics 2001;107(6). Available at http://www.pediatrics.org/cgi/content/hul/107/6/e105. 3. Wiens TE. McSurnett K. Bukstein O. et al. Multisate controlled study of OROS methylphenidate in the treatment of adolescents with Pediatr Adolesc Med. 2006;180:82-90. its with attention-deficitifyperactivity disorder. Arch





He Needs Powerful Efficacy for His Mind But What Will It Do to His Body?





Powerful Efficacy for the Mind

- Every dose proven to effectively control symptoms in every acute pivotal trial (6 weeks)¹
- Demonstrated efficacy over the longer term by delaying time to relapse²
- The first antipsychotic to measure efficacy by improvements in personal and social performance³

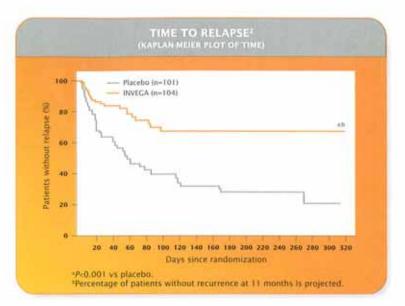
EXPERIENCE THE

Proven Safety and Tolerability for the Body

- Weight gain comparable with placebo in 6-week clinical trials
- EPS rates comparable with placebo in 6-week trials with the recommended 6-mg dose*
- Adverse event type and severity in a longer-term trial were similar to those seen in 6-week pivotal trials

"Total EPS-related adverse events at the 9-mg and 12-mg doses were 25% and 26%, respectively, versus 11% for placebo.



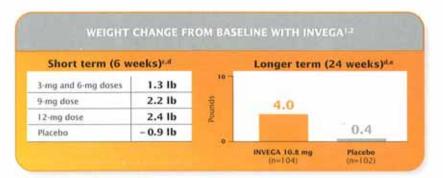


From Kramer et al.

Results from a placebo-controlled study that included a 14-week run-in and stabilization phase, during which patients received INVEGA (3 mg to 15 mg) once daily until they were deemed stable, followed by a double-blind phase in which patients were maintained on a stable dose of INVEGA or given placebo for up to 11 months. The average dose of INVEGA was 10.8 mg (average 24 weeks). The trial was ended at a predetermined interim analysis due to occurrence of a total number of relapses between the 2 groups (mean duration of therapy with INVEGA and placebo was 74 days and 56 days, respectively). 22



BENEFITS OF INVEGA



Data on file and adapted from Kramer et al.

Pooled results from three 6-week pivotal trials.

"The proportion of patients gaining ≥7% of body weight with INVEGA was 7% (3 mg), 6% (6 mg), 9% (9 mg), and 9% (12 mg) versus 5% (placebo) in 6-week trials, and 20% (average 10.8 mg) versus 12% (placebo) in a longer-term, flexible-dose trial.

Results from a longer-term trial of up to 11 months (average 24 weeks that includes a 14-week run-in and stabilization phase). The average dose of INVEGA was 10.8 mg.

Please see Important Safety Information, including Boxed Warning, on adjacent page.

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



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. INVEGATM (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 acute and maintenance 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. INVEGATM (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 OT 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 (moxilloxacin 40) mg single dose, multicenter QT study in addits with schizophenia and schizophenia flored. multicenter QT study in adults with schizophrenia and schizoalfective 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** (Comme 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 Comme 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 mase (90% Ct; 3.6; 10.1) on day 2 at 1.5 hours post-dose. Note the subjects had a change expedition 60 mase or a QTCLD exposition 500 mass of the subjects had a change expedition 50 mass or a QTCLD exposition 500 mass. placebo-subtracted OTCLD of 6.8 misec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 misec or a OTCLD exceeding 500 misec 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 misec at one time-point on Day 6 (increase of 62 misec). No subject receiving INVEGA™ had a OTCLD exceeding 500 misec at any time in any of these three studies. Neuroleptic Malignant Syndrome: A potentially fattal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrews, muscle rigidity, altered mental status, and evidence of autonomic instability. Other signs may include elevated creatinine phosphokingase. 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 atypical antipsychotics. Patients with an established diagnosis of diabetes melitius who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes melitus (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 INVEGATM tablet is non-deformable and does not appreciably change in shape in the gastrointestinal fact, INVEGATM should ordinarily not be administered to patients with pre-existing severe gastrointestinal narct, investing pathologic or latrogenic, for example: esophageal mobility disoorders, 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-refease known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet. INVEGATM should only be used in patients who are able to swallow the tablet whole (see PRECAUTIONS: Information for 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 of tract. Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis: In placebo-controlled trials with risperidone, aripiprazole, and otanzapine 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 poled 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 anispsycholocidings, investor "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_s receptors, paliperidone elevates protactin levells 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 protectin than other antipsychotic drugs. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving protactin-elevating compounds. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplastia (mammary adenocarcinomas, pituitary and pencreatic 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 huma association between chronic administration or tims class or drugs and tumorigeness in numaria, but the available evidence is too limited to be conclusive. Dysphagia: Esophageal dysmotility and aspiration have been associated with antiposychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. INVEGA™ and other antiposychotic 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 sodation 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 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 patiperidone therapy does not adversely affect them. Priapism: No cases of priapism have been reported in clinical trials with INVEGAT¹⁶. 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 INVEGAT²⁶ 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 patientson. 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, antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical feature consistent with the neuroleptic matignant 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 Supposed Information for Patients: Provinciase are artised to discuss the following issues 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-flower. 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 INVEGAT^M 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 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 tirve microsomes showed that paliperidone does not substantially inhibit the metabolizem 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 metabolize pathways in a clinically relevant CYP2U6, 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™.

Orthostatic Hypotension and Syncope). Potential for Other Drugs to Affect INVEGA™. administered with other therapeutic agents that have this potential (see PHECAD) RONS: 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 witro studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, in wive 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

INVEGA™ (paliperidone) extended-release tablets is indicated for the acute and maintenance treatment of schizophrenia.

IMPORTANT SAFETY INFORMATION FOR INVEGA

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, INVEGATM (paliperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

Commonly observed adverse events: The most commonly observed adverse events, occurring at an incidence of ≥5% and at least 2 times placebo, were akathisia and extrapyramidal disorder.

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 of 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. 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.

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 dementiarelated psychosis taking atypical antipsychotics in clinical trials. INVEGA is not approved for treating these patients.

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

Hyperprolactinemia: As with other drugs that antagonize dopamine D₂ receptors, INVEGA elevates 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 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 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 has the potential to impair judgment, thinking, or motor skills. Caregivers and patients should use caution until they are reasonably certain that INVEGA does not affect them adversely.

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

References: 1. Data on file. Janssen, L.P., Titusville, NJ. 2. Kramer M. Simpson G. Maciulis V, et al. Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia; a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol.* 2007;27(1):6-14. 3. Kane J. Canas F. Kramer M, et al. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. *Schizophr Res.* 2007;90:147-161.

recommended human dose of risperidone on a mg/m2 basis (see risperidone package insert). An recommended number dose or hisperitode on a might basis (see risperitoris package itser), increase in mammary, plutilary, 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 D₂ 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 ryseptolacinienia), managenesis, the evidence or generous potential for pasperioone 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 lemale 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 or 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 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 noonate. 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 tumens 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-leed infants. Pediatric Use: Safety and effectiveness of INVEGA™ in patients < 18 years of age have not been established. Geriatric Use: The safety. In patients 2 to years or age into this cere established. General order to describe the 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 INVEGATM (3 to 15 mg once daily, see CLINICAL PHARMACOLOGY Clinical Table in full and INVEGA** (3 to 15 mg once daily, see CLINICAL PHARMACOLOGY: Clinical finish in full PI).

Overall, of the total number of subjects in clinical studies of INVEGA** (n = 1796), including those who received INVEGATM 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™ to the treatment of schizophrenia. Of these 2720 patients, 2054 were patients who received INVEGA™ white 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-thind phases of studies, inpatients and outpatients, fixed dose and fixe/tibe-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 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 vorsened while receiving therapy following baseline evaluation. The information presented in these sections was derived from pooled data from the three placebo-controlled, 6-week, fixed-dose study in which subjects received INVEGA™ at daily doses within the recommended range of 3 to 12 mg (n = 850). 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 with

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 INVEGATM incidence was equal to or less than placebo are not listed in the table, but included the following: constipation, diarrhea, vomiting, nasopharyngilis, 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 in the pooled data from three placebo-controlled, 6-week, fixed-dose studies, 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 9, 11, 3, 15, 14; Akathisia 9 6, 6, 4, 7, 9; Use of anticholinergic medications 10, 10, 9, 22, 22: ": 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). For Akathisia, percent of patients with Barnes Akathisia Rating Scale global score ≥ 2. 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, Hyporkinesia. Muscle rigidity, Musculoskeletal stiffness, Parkinsonism. Tremor group includes: Temor, Adverse Events Associated with Discontinuation of Treatment in Controlled Clinical Studies: Based on the pooled data from the three placebo-controlled, 6-week, fixed dose studies, there 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 Were similar for the INVEGA. "and placebo-heated subjects, except for retrivides dysident placebo-bleared subjects (2% and 0%, respectively), and Psychiatric Disorders events which were more common among placebo-treated subjects than INVEGA™-freated 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 Attack of the three placebo-controlled, 6-week, fixed-dose studies, between-group comparisons revealed no medically important differences between INVEGATM and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine hematology, urnalysis, 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 INVEGAth 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 INVEGATM 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 those issed in table 1 above or elsewhere in tabelling, (2) mose for which a causal relationship to INVEGA!" use was considered remote, and (3) those occurring in only one subject freated 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; info 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 dyspinea; rare: pulmonary embolus; Vascular Disorders: rare: ischemia, venous thrombosis; The safety of INVEGATM was also evaluated in a long-term trial designed to assess the maintenance of effect with INVEGA™ in adults with schizophrenia (see CLINICAL PHARMACOLOGY: Clinical Trials in full PI). In general, adverse event types, frequencies, and severities during the initial 14-week open-label phase of this study were comparable to those observed in the 6-week, placebo-controlled, fixed-dose studies. Adverse events reported during the long-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase. 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.

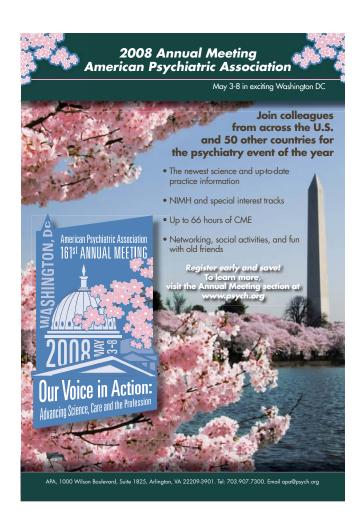
For more information on symptoms and treatment of overdosage, see full Prescribing Information.

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Issued: April 2007

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Call for Nominations

The Institute of Living/Hartford Hospital is pleased to announce that nominations are now being accepted for the 2008 C. Charles Burlingame Award. This

award, honoring an outstanding leader in psychiatric education, research or administration, is made in the memory of Dr. Burlingame, psychiatrist-in-chief from 1931 to 1950.

We invite you to nominate a person who has significantly advanced the field of psychiatry. The nomination must include a current curriculum vitae and two letters of support describing the candidate's achievements.

The winner of the Burlingame Award will be notified by February 15, 2008, and invited to present an original paper as the focal point of the award day events. The award, which will be presented at The Institute in the fall of 2008, includes a commemorative certificate and a \$2500 honorarium plus expenses.

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HARTFORD HOSPITAL

Nominations should be sent no later than January 15, 2008 to: Harold I. Schwartz, M.D. Psychiatrist-in-Chief and Vice-President, Behavioral Health The Institute of Living/Hartford Hospital 200 Retreat Avenue

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It's worse this time. She flies into rages for no reason.

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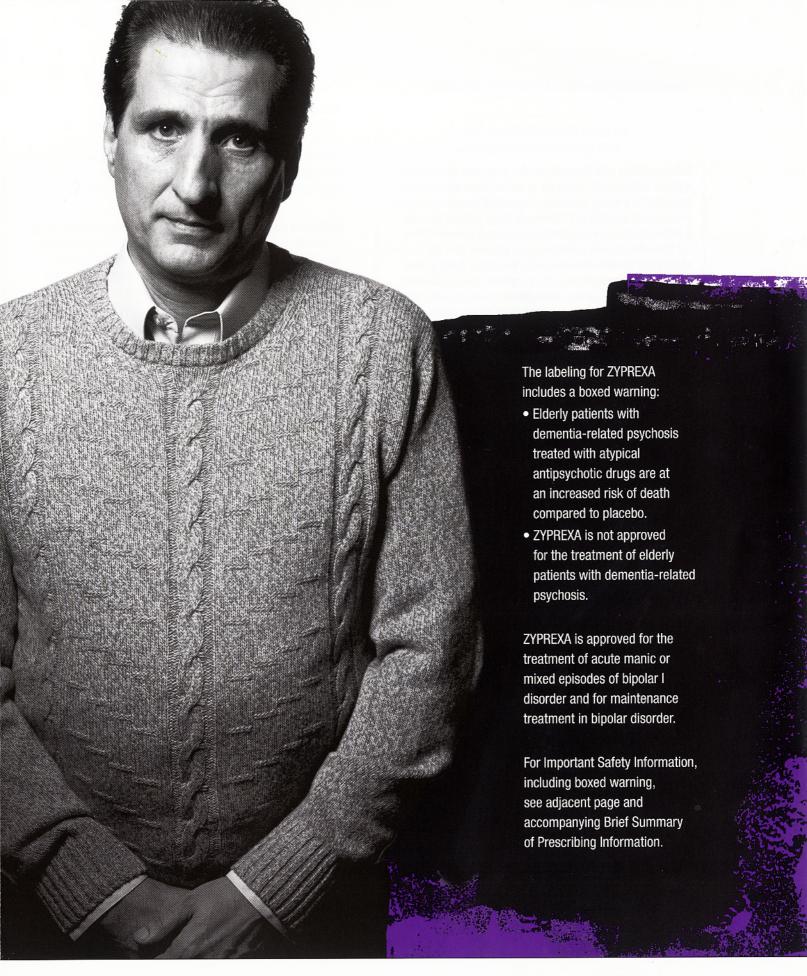
Her thoughts seem to go in a million directions. She says she feels worthless.

This can't go on much longer. It's tearing us apart.

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ZYPIEXA Olanzapine

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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 drugtreated 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. ZYPREXA is not approved for the treatment of elderly patients with dementia-related psychosis.

Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia—Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported in patients in trials of ZYPREXA in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of CVAE in patients treated with ZYPREXA compared to patients treated with placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and diabetes mellitus—Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ZYPREXA. All patients taking atypicals should be monitored for symptoms of hyperglycemia. Persons with diabetes who are started on atypicals should be monitored regularly 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 during treatment should undergo fasting blood glucose testing.

Neuroleptic malignant syndrome (NMS)—As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended. 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 creatinine phosphokinase, myoglobinuria (rhabdomyolysis). and acute renal failure.

Tardive dyskinesia (TD)—As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Medication dispensing and prescribing errors have occurred between ZYPREXA® (olanzapine) and Zyrtec® (cetirizine HCI). These errors could result in unnecessary adverse events or potential relapse in patients suffering from schizophrenia or bipolar disorder. To reduce the potential for dispensing errors, please write ZYPREXA clearly.

The most common treatment-emergent adverse events associated with ZYPREXA (vs placebo) in 3- and 4-week bipolar mania trials were:

somnolence (35% vs 13%) dizziness (18% vs 6%) constipation (11% vs 5%) increased appetite (6% vs 3%) dry mouth (22% vs 7%) asthenia (15% vs 6%) dyspepsia (11% vs 5%) tremor (6% vs 3%)

Common and significantly different adverse events in a 47-week bipolar mania study of ZYPREXA vs divalproex:

somnolence (46.4% vs 24.6%) weight gain (24.8% 11.9%) increased appetite (13.6% vs 5.6%) nervousness (12.0% vs 22.2%) manic reaction (3.2% vs 10.3%)

dry mouth (34.4% vs 7.1%) nausea (16.0% vs 31.7%)

Other treatment-emergent adverse events reported in 5-10% of patients and significantly greater for ZYPREXA or divalproex included akathisia (9.6% vs 1.6%) and rectal disorder (0%vs 5.6%).

The most common treatment-emergent adverse event (reported in ≥5% of patients) with ZYPREXA vs lithium in a 12-month bipolar maintenance trial was depression NOS (20.7% vs 11.7%). Also observed (ZYPREXA vs lithium) were:

insomnia (7.8% vs 22.4%) weight gain (6.5% vs 4.7%) depressed mood (4.6% vs 1.4%)

mania (7.8% vs 20.6%) anxiety (5.5% vs 6.5%)

Discontinuation rates due to adverse events were 18.9% for the olanzapine group and 25.7% for the lithium group (P=.105).

For complete safety profile, see the full Prescribing Information.

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ZYPREXA® (Olanzapine Tablets)

ZYPREXA® ZYDIS® (Olanzapine Orally Disintegrating Tablets)

ZYPREXA® IntraMuscular (Olanzapine for Injection)

Brief Summary: Please consult package insert for complete prescribing information.

MARNING

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. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis.

INDICATIONS AND USAGE: ZYPREXA and ZYPREXA Zydis are indicated for short- and long-term treatment of schizophrenia, for acute manic and mixed episodes of bipolar I disorder, and for maintenance treatment in bipolar disorder. The use of ZYPREXA for extended periods should be periodically re-evaluated as to the long-term usefulness of the drug for the individual patient. ZYPREXA IntraMuscular is indicated for treatment of agitation associated with schizophrenia and bipolar I mania.

CONTRAINDICATIONS: Known hypersensitivity to olanzapine.

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. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis and patients with dementia-related psychosis (and PDY WARDING).

with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis (see BOX WARNING).

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients (3.5%) was significantly greater than placebo-treated patients (1.5%).

Cerebrovascular Adverse Events. Including Stroke, in Elderly Patients with Dementia—Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine 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 olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. Hyperglycemia and Diabetes Mellitus—Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes in patients with schizophrenia and the increasing incidence of diabetes should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes who are starting treatment with atypicals should have fasting blood glucose (FBG) testing at baseline and periodically during treatment. Any patient treated with atypicals should be monitored for symptoms of hyperglycemia. Neuroleptic Malignant Syndrome. (NMS)—Potentially fatal NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. See complete prescribing information of mormation on management of MMS. Patients requiring antipsychotic dr

Although the prevalence of 1D appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are more likely to develop the syndrome. If signs and symptoms of TD appear, consider drug discontinuation.

PRECAUTIONS: Hemodynamic Effects—Olanzapine may induce orthostatic hypotension associated with dizziness; achycardia; and in some patients, syncope. Hypotension, bradycardia with/without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. Incidence of syncope was 0.6%, 15/2500 with oral olanzapine in phase 2-3 trials and 0.3%, 2/722 with intramuscular olanzapine for injection in clinical trials. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine) resident in the sequence of events may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. Patients should remain recumbent if drows or dizzy after injection with intramuscular olanzapine for injection until examination has indicated they are not experiencing postural hypotension, bradycardia, and/or hypoventilation. Olanzapine 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 (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put them at increased medical risk. Caution is necessary in patients receiving treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or CNS depression (see Drug Interactions)

evenu in premarkeung trais (olanzapine 26% vs placebo 15%). Somnolence led to discontinuation in 0.4% (9/2500) of patients in the oral premarketing database.

Body Temperature Regulation—Use appropriate care when prescribing olanzapine for patients who will be experiencing conditions that may contribute to an elevation in core body temperature.

Dysphagia—Esophageal dysmotify 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 disease. Olanzapine 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 schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management.

Use in Patients with Concomitant Illnesses—Olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In 5 placebo-controlled studies in elderly patients with dementia-related psychosis (n=1184), these treatment-emergent adverse events were reported with olanzapine at an incidence of ≥2% and significantly treater than with placebo: falls, somnolence, peripheral edema, abnormal galt, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth, visual hallucinations. Discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for treatment of patients with dementia-related psychosis. If the prescriber elects to treat this patient population, vigilance should be exercised (see BOX WARNING and WARNINGS).

Because of the risk of orthostati

ZYPREXA® (Olanzapine Tablets) ZYPREXA® ZYDIS® (Olanzapine Orally Disintegrating Tablets) ZYPREXA® IntraMuscular (Olanzapine for Injection)

PV 5197 AMP

Information for Patients—See full prescribing information for information to discuss with patients taking

Laboratory Tests—Periodic assessment of transaminases is recommended in patients with significant henatic disease

Drug Interactions—Use caution when olanzapine is taken in combination with other centrally acting drugs and alcohol. Olanzapine may enhance the effects of certain antihypertensive agents. Olanzapine may antagonize the effects of levodopa and dopamine agonists. Agents that induce CYP1A2 or glucuronyl transferase enzyme (eg, omeprazole, rifampin) may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems,

potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. A dosage adjustment may need to be considered with specific drugs.

Activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. Single doses of cmetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine. Carbamazepine (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance. Neither ethanol (45 mg/70 kg single dose) had an effect on olanzapine pharmacokinetics. Fluoxetine at 60 mg (single or multiple doses) causes a small increase in the Cmax of olanzapine and a small decrease in olanzapine clearance; however, the impact of this factor is small comparison to the overall variability between individuals, and dose modification is not routinely recommended. Fluoxamine decreases the clearance of olanzapine; lower doses of olanzapine should be considered in patients receiving fluoxamine concomitantly. In vitro data suggest that a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

comparison to the overall variability between individuals, and dose modification is not routinely recommended. Fluvoxamine decreases the clearance of olanzapine; lower doses of olanzapine should be considered in patients receiving fluvoxamine concomitantly. In vitro data suggest that a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Olanzapine is unlikely to cause clinically important drug interactions mediated by the enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Single doses of olanzapine did not affect the pharmacokinetics of imiparamine/desipramine or warfarin. Multiple doses of olanzapine did not affect the pharmacokinetics of imiparamine/desipramine or warfarin. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites. Co-administration of either diazepam or ethanol potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites. Co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone (see Hemodynamic Effects).

Carcinogenesis, Mutagenesis, Impairment of Fertility—The incidence of liver hemangiomas and hemangiosarcomas in female mice was significantly increased in one carcinogenicity study at 2 times the maximum human daily oral dose (MHDOD) but not in another study at 2-5 times the MHDOD (mg/m² basis). In this study there was a high incidence of early mortalities in males in the 30/20 mg/kg/d group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice and rats given olanzapine at 0.5 and 2 times the MHDOD respectively (mg/m² basis). In other studies, serum prolactin measurements of olanzapine showed elevations up to 4-fold in rats at the same doses used in the carcinogenicity studies. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rod

ADVERSE REACTIONS: The following findings are based on a clinical trial database consisting of 8661 patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection, including patients with schizophrenia, bipolar mania, or Alzheimer's disease (oral olanzapine trials) and patients with agitation associated with schizophrenia, bipolar lidisorder (manic or mixed episodes), or dementia (intramuscular olanzapine for injection trials). See the full prescribing information for details on these trials. Certain portions of the discussion below relating to dose-dependent adverse events, vital significant portions weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania or agitation; however, this information is also generally applicable to bipolar magic and adiation. to bipolar mania and agitation.

and have not been duplicated for Ippolar mania or agitation; however, this information is also generally applicable to bipolar mania and agitation.

Associated with Discontinuation—Overall there was no difference in discontinuations due to adverse events in placebo-controlled oral olanzapine trials (olanzapine vs placebo: schizophrenia, 5% vs 6%; bipolar mania monotherapy, 2% vs 2%; bipolar mania cotherapy, 11% [olanzapine plus lithium or valproate] vs 2% [lithium or valproate] vs 2% [lithium or valproate alone]); or in placebo-controlled intramuscular olanzapine for injection of the placebo 0%, Discontinuations in oral schizophrenia trials due to increases in SGPT were considered to be drug related (olanzapine 2% vs placebo 0%; see PRECAUTIONS).

Commonly Observed Adverse Events—In 6-week, placebo-controlled, premarketing schizophrenia trials, the most common treatment-emergent adverse events associated with oral olanzapine (incidence ≥5% and olanzapine incidence at least twice that for placebo) were: postural hypotension, constipation, weight sail adverse events personality disorder (COSTART term for nonaggressive objectionable behavior), and akathisia. In 3- and 4-week placebo-controlled bipolar mania monotherapy trials, the most common treatment-emergent adverse events observed with olanzapine plus lithium or valproate were divont, the proposition of the placebo controlled trials of intramuscular olanzapine for injection for agitation associated with schizophrenia or bipolar mania, sommolence was the one adverse event observed at an incidence of ≥5% and at least twice that for placebo-controlled rinjection 6%, placebo 3%).

amilesia, and pateriesia. In 2-4-10th placeboc-controlled trials of intransiscular obtainscular obtainscular of an agriation associated with schizophrenia or bipolar mania, somnolence was the one adverse event observed at an incidence of ≥5% and at least twice that for placebo (olanzapine for injection 6%, placebo 3%).

**Adverse Events with an Incidence of ≥2% in Oral Monotherapy Trials—The following treatment-emergent events were reported at an incidence of ≥2% with oral olanzapine (doses ≥2.5 mg/d), and at a greater incidence with olanzapine than with placebo in short-term placebo-controlled trials (olanzapine N=532, placebo N=294):

**Body as a Whole—accidental injury, asthenia, fever, back pain, chest pain; Cardiovascular postural hypotension, tachycardia, hypertension; **Digestive—dry mouth, constipation, dyspepsia, vomiting, increased appetite; **Hemic and Lymphatic—ecchymosis; **Metabolic and Nutritional—weight gain, peripheral edema; **Musculoskeletal—extremity pain (other than joint), joint pain; **Nervous System—somnolence, insomnia, dizziness, abnormal gait, tremor, akathisia, hypertonia, articulation impairment, **Respiratory—rhinitis, couple increased, pharyngitis. **Special Senses—amblyopia; tragential—innary incontinence, urinary tract infection. **Adverse Events with an Incidence of ≥2% with oral olanzapine (doses ≥5 mg/d) plus lithium or valproate (N=29) and at a greater incidence than with placebo plus lithium or valproate (N=115) in short-term placebo-controlled trials: **Body as a Whole—asthenia, back pain, accidental injury, chest pain; **Cardiovascular—hypertension; **Digestive—dry mouth, increased appetite, thirst, constipation, increased salivation; **Metabolic and Nutritional—weight gain, peripheral edema, edema, **Nervous System—somnolence, tremor, depression, dizziness, speech disorder, amnesia, paresthesia, apathy, confusion, euphoria, incoordination; **Respiratory—pharyngitis, dyspnea; **Skin and Appendages—sweating, acne, dry skin; **Special Senses—amblyopia, abnormaly vision; **

Skin and Appendages—sweating, acne, dry skin; Special Senses—amblyopia, abnormal vision; Urogenital—dysmenorrhea, vaginitis.

Adverse Events with an Incidence ≥1% in Intramuscular Trials—The following treatment-emergent adverse events were reported at an incidence of ≥1% with intramuscular olanzapine for injection (2.5–10 mg/lnjection and at incidence greater than placebo in short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania: Boly as a Whole—asthenia; Cardiovascular—hypotension, postural hypotension;
Nervous System—somnolence, dizziness, tremor.
Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms:
In an acute-phase controlled clinical trial in schizophrenia, there was no significant difference in ratings scale incidence between any dose of oral olanzapine (52-5, 10±2.5, or 15±2.5 mg/d) and placebo for parkinsonism (Simpson-Angus Scale total score >3) or akathisia (Barnes Akathisia global score ≥2). In the same trial, only skathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significantly greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence of patients reporting any extrapyramidal event was significantly greater than placebo only with the

highest dose of oral olanzapine (15±2.5 mg/d). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

Other Adverse Events: Dose-relatedness of adverse events was assessed using data from this same clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with

Clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, sonnolence, termor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations >24.2 ng/mL (female) or >18.77 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and dizziness, 20 vs 40 mg/d.

Mital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials (see PRECAUTIONS).

Weight Gain—In placebo-controlled 6-week schizophrenia studies, weight gain was reported in 5.6% of oral olanzapine patients (average 2.8-kg gain) compared to 0.8% of placebo patients (average 0.4-kg loss); 29% of olanzapine patients gained >7% of their baseline weight, compared to 3% of placebo patients. During continuation therapy (238 median days of exposure), 55% of patients met the criterion for having gained >7% of their baseline weight. Average gain during long-term therapy was 5.4 kg. Laboratory Changes*—Olanzapine is associated with olanzapine in the premarketing database. In clinical trials among olanzapine-treated patients with baseline random triglyceride levels of 150 mg/d (10.4650). 63 exposinged trighe cert in the baseline random triglyceride levels of 150 mg/d (10.4650). 63 exposinged trighe cert in the case of the properties of the prop

In clinical trials among olanzapine-treated patients with baseline random triglyceride levels of <150 mg/dL (N=659), 0.5% experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean triglyceride increase of 20 mg/dL Intese salite thats, olarizapine-treated patients (w=1 ras) had a lineal highyedire increase of 20 high the form a mean baseline of 175 mg/dL. In placebo-controlled trials, olarizapine-treated patients with baseline random cholesterol levels of <200 mg/dL (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during the trials more often than placebo-treated patients (N=602; 3.6% vs 2.2% respectively). In these same trials, olarizapine-treated patients (N=602; 3.6% vs 60.4 mg/dL in cholesterol from a mean baseline of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean baseline of 203 mg/dL. baseline of 203 mg/dL

baseline of 203 mg/dL.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant oblazapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥ I mg/d in clinical trials (8661 patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. Frequent events occurred in =1/100 patients; Interquent events occurred in 1/1000 patients, Interquent: abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, enck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; Rare: chills and fever, hangover effect, sudden death. Cardiovascular—Frequent: hypotension; Infrequent: atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, pallotradin, vascodilatation, ventricular extrasystoles; failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; Rare: arteritis, heart failure, pulmonary embolus. **Digestive**—Frequent: flatulence, increased salivation, thirst; Infrequent: dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, inist, imiequent. Osphagia, esophagia, encetal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. *Endoerine—Infrequent:* diabetic acidosis, goiter. *Hemic and *Lymphatic—Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia, *Rare:* normocytic anemia, thrombocythemia. *Metabolic and Nutritional—Infrequent:* acidosis, alkaline* Rare: normocytic anemia, thrombocythemia. Melabolic and Nutritional—Infrequent: acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hypoerijeemia, hypoerucemia, hypoglycemia, hypoeratemia, hypoproteinemia, ketosis, water intoxication, Musculoskeletal—Frequent: joint stiffness, twitching: infrequent: arthritis, arthrosis, leg cramps, myasthenia; Rare: bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. Nervous System—Frequent: abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; Infrequent: akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; Rare: circumoral paresthesia, coma, encephalopathy, neuralgia, vertigo, withdrawal syndrome; Rare: circumoral paresthesia, coma, encephalopathy, neuralgia, encuronathy, nystamus, anarlysis, subarachnoid hemorrhage, tobacco misuse, Resuitator vertigo, withdrawal syndrome; Hare: circumoral parestnesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. Respiratory—Frequent: dyspnea; Infrequent: apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; Rare: atelectasis, hiccup, hypoventilation, lung edema, strior. Skin and Appendage—Frequent: sweating; Infrequent: alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; Rare: hirsutism, pustular rash. Special Senses—Frequent: conjunctivitis; Infrequent: abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; Rare: corneal lesion, elaucoma karatoconjunctivitis macular travpolimentation missis: mydrasis ingment denocitis lesion. inflammatudi, eye pain, ocular insuser adminiarily, asse pervisioni, immus, hate. Comea resour, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. **Urogenital**—Frequent: vaginitis*; Infrequent: abnormal ejaculation,* amenorrhea,* breast pain, cystitis, decreased menstruation,* dysuria, female lactation,* glycosuria, gynecomastia, hematuria impotence,* increased menstruation,* menorrhagia,* metrorrhagia,* polyuria, premenstrual syndrome,* pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged,* vaginal hemorrhage*; Rare: albuminuria, breast enlargement, mastitis, oliguria.

"Addistated for render" (*Adjusted for gender.)

("Adjusted for gender.")

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses \$2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. Body as a Whole—Frequent: injection site pain; Infrequent: abdominal pain, fever. Cardiovascular—Infrequent: Ab Ulook, heart block, syncope. Digestive—Infrequent: claimina pain, fever. Cardiovascular—Infrequent: Ab Ulook, heart block, syncope. Digestive—Infrequent: creatine phosphokinase increased, dehydration, hyperkalemia. Metabolic and Nutritional—Infrequent: creatine phosphokinase increased, dehydration, hyperkalemia. Musculoskeleta—Infrequent: twitching. Nervous System—Infrequent: abnormal gait, akathisa, articulation impairment, confusion, emotional tability. Skin and Appendages—Infrequent: sweating. Pastintroduction and temporally (not necessarily) (not necessarily).

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (eg, anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

DRUG ABUSE AND DEPENDENCE: Olanzapine is not a controlled substance.
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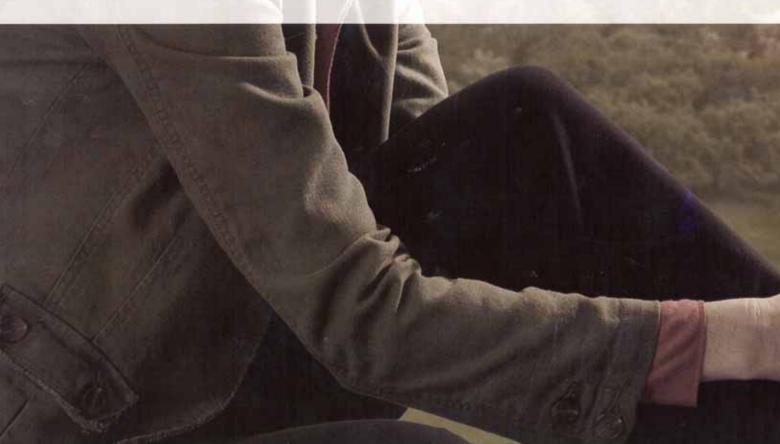
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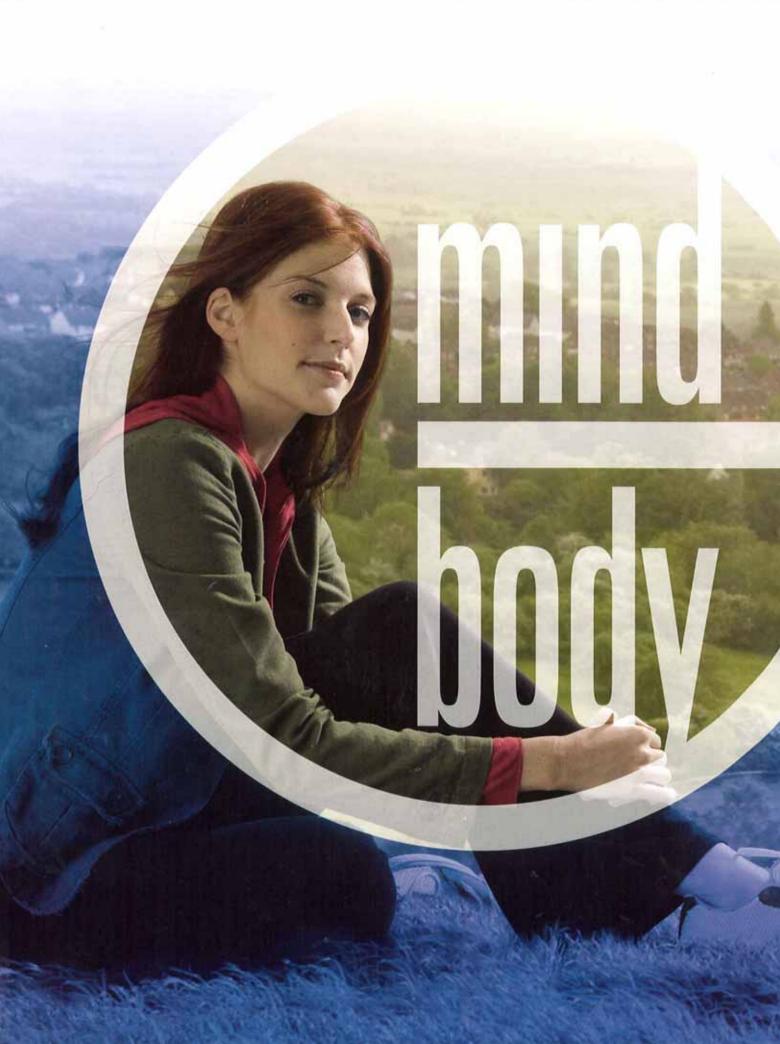
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Because she does not like to compromise...





IN SCHIZOPHRENIA

Treat With the Body in Mind

CHOOSE COMPARABLE POWER...

Consistent results in acute head-to-head studies1-3

BPRS Core Items



Mean % improvement from baseline at end point

A 6-week, double-blind, randomized study of GEODON vs clanzapine 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 risperidone1
 - -up to 6 months vs olanzapines

...WITHOUT COMPROMISING METABOLIC PARAMETERS

Significant results in switch studies after 1 year 1.5



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^a

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 acute manic or mixed episodes associated with bipolar disorder and 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 $_{\rm c}$ 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.

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. 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, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

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 include the risk of rash, orthostatic hypotension, and seizures.

The most common adverse events associated with GEODON in bipolar mania were somnolence, extrapyramidal symptoms, dizziness, akathisia, and abnormal vision.

In short-term schizophrenia trials, the most commonly observed adverse events associated with GEODON at an incidence of ≥5% and at least twice the rate of placebo were somnolence and respiratory tract infection.

In short-term schizophrenia clinical trials, 10% of GEODONtreated patients experienced a weight gain of ≥7% of body weight vs 4% for placebo.



Increased Micrality in Elderly Patients with Dementia-Related Psychosis. Elderly patients with dementia-related psychosis treated with attprical antipsycholic drugs are at an increased frisk of death compared to place bo. Analyses of seventies in placebo controlled trials (model duration of 10 weeks) is threat patients may also also 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 hybrid 10 week controlled trial, the rate of death in drug drusted patients was about 4.5%, compared to a rate of about 2.5% in the placebo group. Although the coases of death were varied, most of the deaths appeared to be either coadiovascular (e.g., heart failure, sudden death) or interclous (e.g., poeumonia) in nature. GEODOM (zigrasidone) is not approved for the breatment of patients with Dementia-Related Psychosis.

INDICATIONS--GEODON Capsules is indicated for the treatment of schloophrents and acute manic or mixed episodes associated with bigolar disorder with or without psychotic features. GEODON* (piprasidone mesylate) for Injection is indicated for acute agitution in

sehkaphenic patients.

CONTRAINDICATIONS — 07 Prologation: Secause of GECOCN's dose-related prologation of the QT interval and the known association of trail armythmas with QT prologation by some other drugs, QECOCN's contraindicated in patients with a known history of QT prologation (including congenital long QT syndrome), with record acute mycordial infanton, or with uncompensated heart failure; see WARNHINGS. I Pharmacokinetic plummacohymnics studies between 6COCOCT and other drugs that prioring the QT instrumed prologation of the part of the prologation of the part of the performed. As additive effect of BEDDON and other drugs that prolong the OT interval cannot be excluded. Therefore, GEODON should not be given with obsticition, social control of the Class is an efficient produced by the Class is an efficient personal per augments by the presence or a metabolic inhibitor (sectionassis zoo mg sod), in placeto-controlled insist, GEOLOW) increased the OT, internal companied to placeto by approximately 10 more at the highest recommended daily does of 160 mg. I clearly with the electrocardiograms of 2/2988 (0.06%) GEODOW patients and 1/440 (0.23%) placebo patients revealed OT, intervals exceeding the potentially clinically relevant threshold of 500 more. In the GEODOM patients, neither case suggested a role of GEODOM. Some defining that prolong the OT/OT, interval have been associated with the courantee of tonsade de pointes and with sodden unsyllained death. The relationship of OT prolongation to tonsade de pointes is clearest for larger increases (20 more and greater) but it is possible that potentially clinically relevant threshold of 500 mise. In the GEODON spatients, neither case suggested a role of GEODON. Some drugs that prolong the OT/OT, internal have been associated with the occurrence of torssed de pointes and with sudden unserplained death. The relationship of OT prolongations to tecsade de pointes is cleared for larger increases (20 mises and with sudden unserplained death. The relationship of OT prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia. hypomagnesemia, or genetic predisposition. Although tessade de pointes has not been observed in association with the use of GEODON at recommended doses in premarkating studies, experience is too limited to rule out an increased risk. A study evaluating the OT/OT, pecilonging effect of istamusous rate (GEODON, with intramusous than halpopried) as a control, was conducted in patient veluriteers. In the trial, ECOs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg than 30 mg) or halpopried of 2.5 mg than 10 mg) given four hours agost. Note that a 30 mg does of internatives a GEODON is 50°, higher than the recommended theraproxic dose. The mean change in OT, from haseline was calculated for each drug using a sample-based correction that removes the effect of head rate on the OT interval. The mean increase in OT, from baseline for GEODON was 4.6 mace following the limit injection and 12.8 mace following the second injection. The mean increase in OT, from baseline for halperided was 6, mmore following the than alternative for days and placeho, sudden unexplained deaths have been reported in patients and placeho. Nevertheless, GEODON is larger prolongation of 0T, league to consider the order of the proposed of the patients of the order of bistory of cardice arrhythmias (see CONTRANDICATIONS, and see Drug Interactions under PRECAMTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrohyte distributances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesumia) may increase the risk of Of prolongation and arrhythmia. Hypokalemia may result from disertic therapy, disurbes, and other causes. Patients with low serum potassium and/or magnesium should be nepticled with those electrohytes before proceeding with treatment. It is essential to periodically monitor serum electrohytes in patients for whom disuretic therapy is introduced during GEODON treatment. Persistently prolonged Of, intervits may also increase the risk of thather prolongation and arrhythmins, but it is not clear that routine screening ECD measures are effective in detecting susch policients. Rather, ECDOON should be avoided in patients with histories of significant conflowascoular interval effects of the prolongation, recent acute myscardial infarction, uncompensate heart tailors, or cardiax arrhythmia. GEODON should be discentinued in patients who are bound to have persistent OT, measurements >500 msec. Neuroleptic Malignant Syndrome (MMS): A potentially that pymptomic complex sometimes referred to as learned gets. Malignant Syndrome (MMS) has been reported in association of astrophyshologic drugs. The manugement of MMS should include (1) immediate discontinuation of antipopychotic drugs and other drugs on desential to concurrent therapy. (2) intensive windows the measurement and medical monotonics and (3) treatment of and the properties of the properties of the properties with the properties of the pr other drugs not essential to concurrent therapy. (2) intensive symptomatic beatment and medical monitoring, and (3) treatment of any concomitant series; medical problems for which specific treatments are available. If a patient requires antispychotic drug beatment in recovery from NMS, the potential entireduction of drug therapy; should be carefully considered. The patient requires antispychotic drug beatment is recovery from NMS, the potential entireduction of drug therapy; should be carefully considered. The patient should be carefully monitored, since recurrences of MMS have been reported. Another bysalinesis (TD): A syndrome of potentially investible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsycholic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women. It is impossible to retly upon prevalence estimates to predict, at the inception of antipsycholic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODOTA, drug discontinuations hould tending in easily, section is selected with a processor of the properties of the animals or processor. It is not known in the football of the continuation of the properties of the processor of the properties of the processor of the properties of the processor o elderly patients, in particular those with advanced Altheimer's dementia, and GEODON and other antipoychotic drugs should be used carbooxy's in patients at risk for approach prejuments. (See also Board WARHING, WARNINGS: Increased Ministry in Electry Warnings with Dementiar Related Psychotics); hyperpeolaticnemic, As with other drugs that antipoprise department of, incoprise of GEODON elevates prolatin levels in humans. Tissue culture experiments indicate that approximately one thirties human breast cancers are protected dependent in vitro, a bactor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancers heard the previous protection of the prescription of these drugs is contemplated in a patient with previously detected breast cancers when the previous previously detected the prescription of these drugs is contemplated in a patient with previously detected breast cancers when the previously detected in the prescription of these drugs is contemplated in a patient with previously detected the previously previously and the previously detected the prescription of the previously one of the previously detected the previously detected the previously protected in the previously detected the previously of the previously one of the previously detected the previously protected in the previously detected the previously of the previously of the previously detected the previously of the previously detected the previously of the previously detected t enough and tumorgeness in humans; the available evidence is considered too limited to be conclusive and Motor Impairment, Sommolence was a postmonely reported adverse event in GEODON patients in the 4- and 6- week placebo continued and some provided in 14% of GEODON patients in 75% of placebo galeria. Sommolence led to disconfinuation in 0.3% of patients in short-term clinical trials. Since GEODON patients in 5% of placebo galeria, Sommolence led to disconfinuation in 0.3% of patients in short-term clinical trials. Since GEODON patients in short-term clinical trials. Since GEODON patients in short-term clinical trials. Since GEODON patients is not received a state of intransactive GEODON prop were breakther (17%), and commolence (20%). Adverse Events at an accident of the lowest intransactive GEODON group were breakther (17%), and commolence (20%). Adverse Events at an accidence 17% is 6EODON group were breakther (17%), and commolence (20%). Adverse Events at an accidence 17% is 6EODON group were breakther (17%), and commolence (20%). Adverse Events at an accidence 17% is 6EODON group were breakther (17%), and commolence (20%). Adverse Events at an accidence 17% is 6EODON group were breakther (17%), and commolence (20%). Adverse Events at an accidence 17% is 6EODON group were breakther (17%), and commolence (20%). Adverse Events at a common accidence 17% is 6EODON group were breakther (17%), and commolence (20%). Adverse Events at a common accidence 17% is 6EODON group were breakther (17%), and commolence (20%). Adverse Events at a common accidence 17% is 6EODON group were breakther (17%), and common accidence 17% is 6EODON group were breakther (17%), and common accidence 17% is 6EODON group were breakther (17%), and common accidence 17% is 6EODON group were breakther (17%), and common accidence 17% is 6EODON group were breakther (17%), and common accidence 17% is 6EODON group were breakther (17%), and common accidence 17% is 6EODON group were breakther (17%), and common accidence 17% is 6EODON group were break

Information and instructions in the Pident Information Sectionshould be discussed with patients. Laboratory Tests: Patients being considered for GEODOM treatment who are at risk of significant electrolyte disturbances should have baseline setum potassium and magnesium measurements. Low serum potassium and magnesium should be replated before treatment. Patients who are found of durance decoded in the measurements of the mea or incompreting passers incorroses concurrences are not invalved by the programment of incorporation of the programment of the state level or renal clearance of lithium. GEDD01 20 mp bit did not affect the pharmacokinetics of concomitantly administrated on orthocoptise, eithiny establic (1003 maj) and levenorepsetel (0.15 mp). Consistent visit in evitor seats, as a tably sin normal try voluntiers, showed that GEDD01 did not after the metabolism of disdometrophan, a CYP206 model substrate, to its major metabolite, destrophan. There was no statistically significant change in the urinary destrometrophan destrophan ratio. Carcinogenesis, Matagenesis Repairment of Perfollity Lithien carcinogenosis, studies were consucted with GEDD01 in long Evens statistically significant change in the urinary destrometrophan destrophan ratio. Carcinogenesis, Matagenesis, the pharmacokin in long terms as an increase in incidence of fumors relative to constrots. In ferrale most there were dose-related increases in the moldences of publicary did adenoma and carcinoma, and mammany gland adenocacionens at all doses steals of increases in sentences of the production of the findings of production endutid destroors unders is unknown to be "phygogosticalismings." Matagenesis. There was a reproduction from the production endutid destroors are statis of 5. Apphirmums in the absence of metabolic acquisition. Positive results were obtained in both the in who mammalian come maturial cassay and the in vitro choromocentral absention assist in films in flowing for the production of the prod tunios in roderts is unknown (see Hyperpostacinemia). Mutagenesis. There was a reproducible mutagenic response in the American of metabolic activation. Postive results were obtained in both the in white mammasian cet gene mutation assay and the in vitro chromosomal aberration assay in human hymphocytes. Impairment of Earthly, GEODON increased time to copulation in Sognapor-Daviley rate in him behalty and early embryoric development studies at bodes of 10 to 850 mg/s/gitty (0 to be times the MiRHO of 200 mg/s/gitty) of 5 to brines the MiRHO of 200 mg/s/gitty (0 to be times the MiRHO on a mg/mir basis). Their exists was reduced. Prepanacy—Prepanacy Calegory C. There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy-only if the potential breath justifies the potential into the him. Labor and Delivery. The effect of GEODON in but and delivery in human is unknown. Marsing Mathems: is not known whether, and if so in what amount, GEODON or its metabolites are increased in human milk. Its recommended that women receiving GEODON should not breast feet. Pediatric bits: The safety and effectiveness of GEODON in pediatric patients have not been established. Gentatric bits: Office approximately 4500 patients between the GEODON in chinal studies. 24% 1509 were 65 years of agree or over, in general, there was no indication of any different identities for technologies of the development of the patients and the compared to younger adults. Nevertheless, the presence of multiple tackors that might increase the pharmacody, numeric response to GEODON in chinal studies. Solve that the solve is metabolic and the solve the solvent and consideration of any different identities for consideration of any discontinual response to the GEODON in chinal studies. Solve them, Placebo-controlled frails: The following hings, are based on the short-term placebo-controlled prails in the following the initial design period for some eticity patients. ADVERSE HEACTIONS — Adverse Findings Observed in politims (1%) compared to one placebo politims (an interest of politims (1%) compared to one placebo politims to the remaining adverse events.

Adverse Pepels at an incidence a 5% and at Least Twice the Rate of Placebo: The most commonly observed adverse events associated with GEOOOI in schizophrenia trials were sommoline of (1%), and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEOOOI in bigodin maria trials were sommoline of 3%, activated (1%), and seems (16%), asstances (16%), asstance Some and Appendings—Industry implainment of the second sec Scale did not generally show a difference between GEDDON and placeto. Wtal Sign Changes: GEDDON is associated with orthostatic hypotension (see PRECAUTIONS). Weight Galar in short-term schizophrenia briais, the proportions of patients meeting a weight gain criterion of 2.7% of body veight were compared, evenaling a statistically significantly speater incodere of veighting time of GEDDON patients (10%) as placebo patients (4%). A median weight gain of 0.5 kg was observed in GEDDON patients. During berg-term therapy with GEDDON, a categorization of patients abserbe contributes of body mass index (6%) showed the greatest manw weight gains and the highest incidence of clinically significant weight gain of 1.8% of body weight is patients with a two BMI (-23) compared to normal (23-27) or overweight patients. There was a mean weight gain of 1.4% of to patients with a 16w BMI (-23) compared to normal (23-27) or overweight 5.27 patients. There was a mean weight gain of 1.4% of to patients with a 16w BMI (-23) compared to normal (23-27) or overweight 5.27 patients. There was a mean weight gain of 1.4% of to patients with a 16w BMI (-23) compared to normal (23-27) or overweight 5.27 patients. There was a mean weight gain of 1.4% of to patients with a 16w BMI (-23) compared to normal (23-27) or overweight 5.27 patients. There was a mean weight gain of 1.4% of to patients with a 16w BMI (-23) compared to normal (23-27) or overweight 5.27 patients. However, and the compared to 1.2% between the compared to 1.2% between 1.2% of 1.2 degree AV block, bundie branch block, pielbolis, pulmonary embolus, cardiomegaly, cerebral intarct, cerebrovascular accident, geographicable, impocardisis, thrombophlebilis, Digieshing System—Frequent anorexia, vumiling, Infrequent rectail hemonthage, dyshogals, tongue edemic Rare gum hemorthage, pundon, fecal impaction, gurman glotamyl brancepetidase increased, hemalierinesis, cholesatic juundice, hepatitis, hepatomegaly, feskoptakis of mouth, tany liver deposit, melina: <u>Endocrine—Rare hypothyrotica</u>, hypothyroticas, hypothyroticas, hypothyroticas, hypothyroticas, hypothyroticas, hypothyroticas, verifice, document, hypothyroticas, policyposis, evincophila, lymphadenopathy, Rare thrombocytepenia, hypothyrotica enemia, lymphocytesia, monocytosis, basophilia, lymphedema, polycythemia, trombocytepenia. <u>Metabolic and Manticional Disorders—</u> himpeanet thirest, brancamiane increased, peripheral edemia, hypothyroticas increased, albumienhopholisase increased, albumienhopholisase increased, albumienhopholisase increased, albumienhopholisase increased, inspectionalis. Hypothyroticas in hypothyroticas creatine phosphakinias increased, alkaline phosphatas increased, hyperholesteremia, deflydration, tackic deflydrogenase increased, albuminuria, hypochalemia, Rave BUN increased, cetatrine increased, hyperformia, hypochalemia, hypochalemia,

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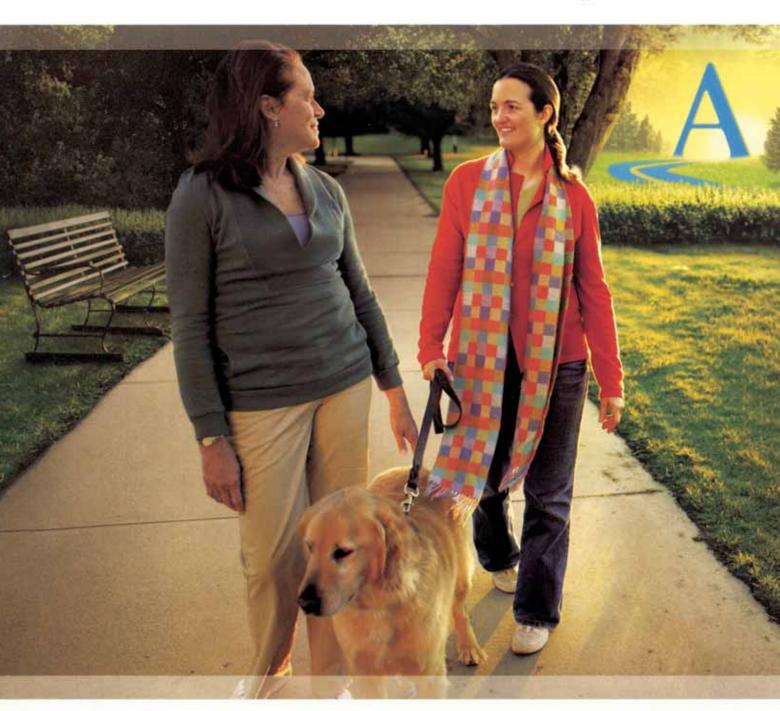
The things that may describe a patient with schizophrenia...

Delusions Emotional withdrawal Disorganized behavior

Family history of high cholesterol

...can obscure the person

ABILIFY Helps Reveal

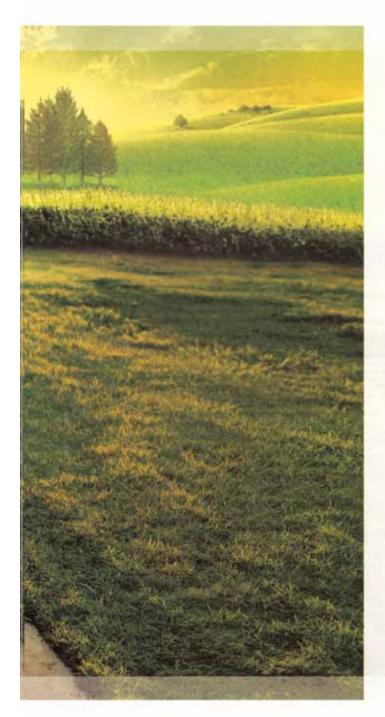


ABILIFY is indicated for the treatment of schizophrenia.

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.

HELP ILLUMINATE

The Person Within.



Meet Kristen, age 31. She is a patient with schizophrenia, but she's also an animal lover, daughter, and friend. She's so much more than her illness.

Do you have someone like Kristen in your practice?

ABILIFY significantly reduced positive and negative symptoms, as measured by PANSS™ Total Score, at primary endpoint (Week 4) in a 4-week, double-blind, placebo-controlled trial in patients with schizophrenia.¹

In a long-term (26-week), placebocontrolled trial there were no medically important differences between the ABILIFY and placebo patients in the mean change from baseline in triglyceride, HDL, LDL, and total cholesterol measurements.

PANSS™ (Positive and Negative Syndrome Scale) is a trademark of Multi-Health Systems, Inc.

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

THE PERSON WITHIN



IMPORTANT SAFETY INFORMATION for ABILIFY

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 for Schizophrenia:

- Rapid control of agitation*
- Early and sustained positive and negative symptom control
- Low incidence of somnolence/sedation[†]
- Low mean weight change in clinical trials
 - In a 52-week schizophrenia trial, weight change averaged 1 kg for ABILIFY-treated patients (BMI <23, 2.6 kg; BMI 23 to 27, 1.4 kg; BMI >27, -1.2 kg). 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.
- Lipid profile comparable to placebo

*With ABILIFY Injection at primary endpoint (2 hours). ABILIFY Injection is indicated for the treatment of agitation associated with schizophrenia.

*As early as Week 1 through study endpoint (Week 4).

*ABILIFY 10%, placebo 8%.

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

Like other antipsychotics, ABILIFY may have the potential to impair judgment, thinking, or motor skills. Patients should not drive or operate hazardous machinery until they are certain ABILIFY does not affect them adversely.



HELP ILLUMINATE THE PERSON WITHIN

Please see BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on adjacent pages.

Reference: 1. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizoaffective disorder. Arch Gen Psychiatry. 2003;60:681-690.

Rx only

ABILIFY® (aripiprazole) TABLETS

ABILIFY® (aripiprazole) ORAL SOLUTION

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INCREASED MORTALITY IN FLOERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

RICHEASED MORITALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED STATUSIS.

Elderly patients with dementia-related psychosis treated with abplical 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: <u>Increased Mortality in Elderly Patients With Dementia-Related Psychosis</u> - Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ABILITY (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 ABILIPY. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, aftered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhytmia). 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 artipsychotic 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 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 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 possible 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-Psychosts: In placebr-controlled clinical studies (with lexible-locks and their insert-does study) or definition 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, BullIPr's 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 hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including ABILIPY. 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:

PRECAUTIONS: General:
Orthostatic Hypotension: ABILIFY may be associated with orthostatic hypotension, perhaps due to its c₁-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 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 mmlgl 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. sedation and for orthostatic hypotension.

Seizures: In short-term trials, seizures/convulsions occurred in 0.1% (1/926) of oral aripiprazole-treated Seizures: In sign1-rel mails, seque exconvisions occurred in 0.1% (1/320) of oral aripphazore-reated patients with schizophrenia, in 0.3% (2/597) of oral arippirazole-treated patients with ploploar maina, and in 0.2% (1/501) of arippirazole injection-treated patients with agitation associated with schizophrenia or bipolar maina. Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that 1 lower the seizure threshold may be more prevalent in a population of 65 years or older.

Conditions that lower the selecter direshold may be more prevalent in a population to 63 years of order.

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; and in 9% 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 In three, 10-week, phasebu-controlled studies of amphracole in duely placelled with psychists associated with Alzheimer's dissigne (n=393), the treatment-emergent adverse events that were reported at an incidence of ≥3% and aripharable incidence at least twice that for placebo were lethargy, somnolence (including seation), incontinence (primarily, urinary incontinence) excessive salivation, and lightheradedness. 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 aripiprazole:

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

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

and zou mg of tructose.

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, CYP2C98, CYP2C9, CYP2C19, and CYP2C19 (contemporazole, warfarin), and CYP3A4 (dextromethorphan) substates. 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.

 $\label{eq:Carbamazepine: Coadministration of carbamazepine (200 mg BID) with ABiLIFY (30 mg QD) resulted in an approximate 70% decrease in <math>C_{max}$ and AUC values of aripiprazole and its active metabolite, dehydroaripiprazole.

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 CYP3A0 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, dehydroaripiprazole, 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.

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/m²) to SD rats and 1, 3, and 10 mg/kg/day to 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 adenocarcinomas 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/m²). In female rats, the incidence of mammary gland fibroadenomas was increased at 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/m²), and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (0, 1 times human exposure at MRHD based on AUC and 3 times the MRHD based on omg/m²). 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) produced increases in numerical aberrations in the in wito 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 wer

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.

Certatric 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 (c-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 Anjupizazile has been evaluated for safety in 4-bb patients with participated in histopizaziles, clinical sinchicipated proprienta, 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 Adverse Events Associated with Discontinuation of Treatment Overali, there was interentee 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. 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.

to discontinuation were similar between the oral anapprazole and placebor-treated patients.

Commonly Diserved 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 arripiprazole 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 arripiprazole were: akathisia (15%, 3%), constipation (13%, 6%), sedation (8%, 3%), temor (7%, 3%), restlessness (6%, 3%), extrapyramidal disorder (5%, 2%). In 24-hour placebo-controlled trials of inframuscular arripiprazole 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%), anusaa (16%, 12%), vomiting (12%, 63%), dizziness (11%, 83%), constipation (11%, 7%), dyspepsia (10%, 8%), akathisia (10%, 4%), sedation (7%, 4%), fatigue (6%, 5%), extrapyramidal disorder (6%, 4%), somnolence (5%, 4%), dyn mouth (5%, 4%), artingia (5%, 4%), termor (5%, 3%), restlessness (5%, 3%), paryngolaryngeal pain (4%, 3%), pain in extremity (4%, 2%), cough (3%, 2%), nasal congestion (3%, 2%), abdominal discomfort (3%, 2%), should (3%, 2%), pain (3%, 2%), vision blurred (3%, 1%), silvary 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, myslejia, adiation, psychotic disorder, dysmenorrhea pain, musculoskeletal stiffness, back pain, myalgia, agitation, psychotic disorder, dysmenorrhea (percentage based on gender total), and rash.

(doses 5.25 mg/day) and at 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%), lachycardia (2%, -1%), akathisia (2%, 0%), dyspepsia (1%, <1%), ory mouth (1%, <1%), blood pressure increased (1%, <1%), musculosketia stiffness (1%, <1%). The following events were reported by patients treated with aripiprazole injection with a incidence great to relieve than placebox injection site burning inscriptions to burning inscriptions and instruments. 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%).

the 30 mg/day dose (placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.5%). 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 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 arijipirazole 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 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 to 27, 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 >30 to 27, and 4.2% for those with BMI >32 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 <31, 1.4 kg for those with BMI >32 to 27, and -1.2 kg for those with BMI >32 to 27, and 32 to 32 to 32 to 32 to 33 to 33 to 34 to 34 to 35 to 35

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 interated 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 The following adverse events were reported with oral aripiprazole at multiple doses ≥2 mg/day in clinical rials (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 fewer than 1/1000 patients; infrequent events are those occurring in fewer than 1/1000 patients; infrequent events are those occurring in fewer than 1/1000 patients; infrequent events are those occurring in fewer than 1/1000 patients; infrequent events are those occurring in fewer than 1/1000 patients, Bload and Lymphalis System Disorders: Inrequent evaneamia, lymphadenopathy, leukopenia (including agranulocytosis, neutropenia); Rare - leukocytosis, hrombocytopenia, idiopathic thrombocytopenic purpura, thrombocythaemia. Cardiac Disorders: Frequent etailycardia (including ventricular, spraventricular, sinus); Infrequent - bradycardia, papitations, cardiac failure (including ventricular) and acute), myocardial infarction, cardiac arrest, atrial fibrillation, atrioventricular block (including first fight), myocardial sichaemia; Rare - atrial fittler, cardiomegaly, cardiomyopathy, cardioulumonary failure. Ear and Labyrinth Disorders: Infrequent - ear pain, vertigo, tinnitius; Rare - deafness. Endocrine Disorders: Infrequent - hypothyroidism, Rare - goitre, hyperparathyroidism, hyperthyroidism. Eye Disorders: Frequent - conjunctivitis; Infrequent - eye redness, eye irritation, deel deafness, eye haemortherage. Castorinatestinal Disorders: Frequent - loose stools; Infrequent - flatulence, dysphajia, gastroesophageal reflux disease, culogyration, eyelid obedema, photophobia, diplopia, eyelid prosis, eye haemortherage. Castorinatestinal biso trongue, contis, nemartatenesis, nyperchiontrynal, intrable nowel sylintonien, despingialist, latetas fiato, 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 littery, 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, Polsoning, and Procedural Complications: Frequent - fall, skin laceration, contusion, fracture; Infrequent - bilster, scratch, joint sprain, burn, muscle strain, periorbital haematoma, arthropod bite/sting, head injury, sunburn; Rare - joint dislocation, alcohol poisoning, oad traffic accident, self mutilation, eye penetration, injury asphyvation, poisoning, heat exhaustion, heat stroke. Investigations: Frequent - weight decreased, blood creatine hosphokinase increased, infrequent - blood glucose increased, heart rate increased, bold temperature increased, alanine aminotransferase increased, blood dreatine increased, blood briguish increased, aspartame aminotransferase increased, blood creatine increased, blood urine present, electrocardiogram ST segment abnormal (including depression, elev 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 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 1-wave inversion, hear rate decreased, tuberculin test positive, glucose urine present, glycosylated haemoglobin increased, glycosylated haemoglobin decreased, urine present, glycosylated haemoglobin decreased, muscle enzyme increased. increased, blood potassium increased, neutrophil count decreased, urine output decreased, blood creatine phosphokinase MB increased, EC6 slips of myocardial ischemia, electrocardiogram T-wave inversion, heart rate decreased, tuberculin test positive, glucose urine present, glycosylated haemoglobin increased, glucosy tolerance decreased, glycosylated haemoglobin decreased, muscle enzyme increased, glucose tolerance decreased, glycosylated haemoglobin decreased, muscle enzyme increased, glycosylated intervention of the control of the properties of (including Bushing), 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 (749 patients). This is may find include events perviously used essewhere in the latenting, induce events with 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 at least 1/100 patients, infrequent 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 privitus, injection site systems. Infection to the control of the procurry of the property of the procurry of th Sweining, verinjunicule site utilise. Imberioris and Imbestadoris. Imbequent - bacterioris, ormaly risch 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 drugasseking 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 OVERNOSAGE: 76 cases of behavior at the control of the control of

Management of Overdosage: No specific information is available on the treatment of overdose with Management of Overdosage: No specific information is available on the treatment of overdose with anipiprazole. An electrocardiogram should be obtained in case of overdosage and, if TOE 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

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CHAIR, DEPARTMENT OF PSYCHIATRY & BEHAVIORAL SCIENCES EASTERN VIRGINIA MEDICAL SCHOOL, NORFOLK, VIRGINIA

Eastern Virginia Medical School (EVMS) has initiated a search for a talented leader to Chair the Department of Psychiatry and Behavioral Sciences. The School has made a major commitment to strengthen, expand and integrate its academic programs in clinical and basic sciences and develop an academic culture which places EVMS at the forefront in translational research, education and healthcare delivery. The new Chair of Psychiatry will be provided the needed support to enhance and develop existing and new academic programs that address the mental health care needs of the region. Currently, the EVMS Department of Psychiatry and Behavioral Sciences has 21 full-time faculty and 98 community faculty with affiliations at several training institutions. The Psychiatry Department residency program has 16 residents and is fully-accredited by the ACGME. In addition, the Department houses a highly competitive Psychology Intern program (eight interns) approved by the APA since 1982, a Postdoctoral Fellowship in Neuropsychology and Forensic Psychology (two Fellows), an APA approved doctoral program in Clinical Psychology in collaboration with the College of William and Mary, Old Dominion University and Norfolk State University, and a nationally recognized Art Therapy masters program.

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All inquires, nominations and applications will be held in the strictest confidence and will be reviewed as they are received and continue until the position is filled. Applicants should forward electronically (hubandsb@evms.edu) a letter of interest and Curriculum Vitae addressed to:

> Francis L. Counselman, M.D. Chair, Department of Psychiatry Search Committee Eastern Virginia Medical School PO Box 1980

Norfolk, Virginia 23501-1980

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> Alan D. Valentine, M.D., **Psychiatry Chairman, Ad Interim** c/o Pat Semmelrogge, Sr. Administrative Assistant **UT M. D. Anderson Cancer Center** P.O. Box 301402 - Unit 453 Houston, TX 77230-1402 Fax: (713) 792-8242

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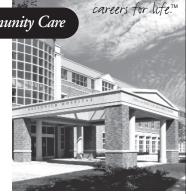
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BILOXI//PENSACOLA/MOBILE Outpatient and Inpatient Psychiatry positions. Expertise in telepsychiatry, substance abuse, geropsychiatry and PTSD preferred. BE/BC psychiatrist, state license (any state), U.S. citizen or permanent resident. Send applications to Jean Williams, HRMS (05A), 400 Veterans Avenue, Biloxi, MS or contact at jean.williams@med.va.gov or (228) 523-5633.

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 7109 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 7109.

FAYETTEVILLE, MT. VERNON Contact Laura Berg, HRMS, at laura.berg2@va.gov or (479) 443-4301, ext 5191.

THE UNIVERSITY of TENNESSEE

HEALTH SCIENCE CENTER

CHAIR DEPARTMENT OF PSYCHIATRY COLLEGE OF MEDICINE

The University of Tennessee Health Science Center College of Medicine seeks a diverse pool of nominees and applicants for the position of Professor and Chair of the Department of Psychiatry. The University of Tennessee Health Science Center is committed to excellence in education, research and service. The Chair of the Department of Psychiatry will oversee all activities of the Department to ensure that the goals and objectives are met as established by the Executive Dean for the College of Medicine. The Chair should be capable of developing an enhanced clinical practice for the Department and of providing energetic leadership and articulation of a vision for the continued growth and development of this major clinical and academic department.

Applicants should hold the M. D. degree or equivalent, be board certified in psychiatry and eligible for licensure in Tennessee upon appointment, and be qualified to be appointed as Professor of Psychiatry. A substantial record of leadership in an academic department of psychiatry is required. The successful candidate will possess leadership abilities collaborating with other basic and clinical department leaders, have knowledge of current professional trends in psychiatry and current trends in the professional and business practices of the health care system, as well as the knowledge to expand the research enterprise by obtaining external grant support within the Department. Applicants should have a demonstrated commitment to and knowledge of equal employment opportunity and affirmative action.

Qualified applicants must submit a letter of interest and qualifications accompanied by curriculum vitae, and the names and addresses of three references to:

Charles R. Handorf, M.D., Ph.D.
Professor and Chair, Department of Pathology
Chair, Psychiatry Chair Search Advisory Committee
The University of Tennessee Health Science Center
P. O. Box 63647
Memphis, TN 38163

Review of applicants will begin immediately and will continue until the position is filled.

The University of Tennessee is an EEO/AA/Title Vi/Title IX/Section 504/ADA/ADEA institution in the provision of its education and employment programs and services.

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Atascadero State Hospital now pays board certified psychiatrists starting at \$216,120 and advancing stepwise to \$247,320. Atascadero is the nation's premier center for the treatment of forensically committed mentally ill patients. Our hospital is a teaching site affiliated with the University of California, accredited by JCAHO, and recipient of the prestigious Codman Award. All of our psychiatrists are board eligible and most are board certified. Many of our psychiatrists have forensic subspecialty boards.

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For a prompt and confidential review, send CV to Jeanne Garcia, M.D., P. O. Box 7001, Atascadero, CA 93423-7001; (805) 468-2005 or fax (805) 468-2138; or e-mail us at jgarcia@ash.dmh.ca.gov.

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ADULT PSYCHIATRY OPPORTUNITY

GEISINGER HEALTH SYSTEM

Geisinger Health System's Division of Psychiatry in Danville, PA, is seeking an adult psychiatrist. This position offers an excellent quality of life and an opportunity to work part-time or full-time depending on the needs of the candidate.

This position offers:

- A flexible schedule start/end times are negotiable, and the specific psychiatric interests and talents of applicants usually can be integrated into the needs of the practice. Opportunities include inpatient – outpatient – emergency – and consultationliaison psychiatry.
- A wonderfully collaborative team of psychiatrists/psychologists with experience and expertise in a variety of psychiatric specialties.
- The support of multiple PAs, a nurse specialist and masterslevel therapists.
- An excellent call schedule (1 in 7), most call via telephone from home.
- The opportunity to work in a comprehensive academic practice that sees a wide variety of clinical activity from pediatric to geriatric patients and diagnostic types and treatments (including ECT).
- Research opportunities through the Weis Center for Research and Geisinger Center for Health Research (both located on the campus of Geisinger Medical Center). Current research projects include studies on genomic schizophrenia, adolescent depression and improving the delivery of adult depression through primary care.
- An accredited Clinical Psychology Internship and the opportunity to teach pediatric and emergency medicine residents, as well as third year medical students from Temple University and Pennsylvania College of Osteopathic Medicine, with clinical appointments available.
- An established referral base through Geisinger Health System's 40 community medical groups, 3 hospitals, local/community physicians and the broad-base of third party contracts.

In the past two years Geisinger's Department of Psychiatry has added a 10-bed Adolescent Inpatient Unit at Geisinger South Wilkes-Barre, the neuro-psychiatry practice has doubled and added 2 post-doctoral fellows and Pediatric Psychiatry has experienced significant growth. At Geisinger, you'll experience the support, camaraderie and professional challenges of a leading practice while discovering the charms of Pennsylvania living... all while having the time and flexibility to enjoy your new quality of life.

To discuss this opportunity, contact: Kathy Kardisco, Recruiter, Geisinger Dept. of Pro. Staffing, 100 North Academy Avenue, Danville, PA 17822-2428 Phone: 1-800-845-7112 • Fax: 1-800-622-2515 e-mail: kkardisco@geisinger.edu

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VA Salt Lake City Health Care System

VASLCHCS is affiliated with the University of Utah School of Medicine, seeks a full time BC/BE staff psychiatrist. The primary duty will be to provide psychiatric medication management to patients in satellite clinics utilizing telepsychiatry. Limited overnight travel to outlying clinics may be required.

Applicants must qualify for academic appointment at University of Utah School of Medicine. Academic appointment will be commensurate with experience and may be adjunct or in the full time clinical or tenure track. Opportunities exist to teach and supervise medical students and psychiatry residents. On-call requirements are minimal.

The VA Salt Lake City Health Care System offers excellent benefit programs. Must be U.S. Citizen. Closes once position is filled.

Send CV and names/addresses of three references to:

VA Salt Lake City Health Care System
Human Resources (Mail Code 05C)
Salt Lake City, Utah 84148
Attn: Tonya Mackintosh
Reference Announcement #C07-246.
For additional information contact Tonya Mackintosh at 1-801-584-1284, ext. 2267 or Nikki Morris, ext. 4403.

Equal Opportunity Employer

San Francisco Bay Area

Santa Clara Valley Health and Hospital
Systems is looking for full and part-time
BC/BE psychiatrists to staff outpatient
specialty services, inpatient psychiatric
units, custody psychiatric services, and the
psychiatric emergency room. Contract physician positions available. All positions
available immediately. Very competitive
compensation package.

Current California licensure is
mandatory.

C.V. to:

Michael Meade, MD, Chairman Department of Psychiatry 871 Enborg Court San Jose, California 95128 Phone: 408.885.6122 FAX: 408.885.6126

We are a full service training campus, affiliated with Stanford University

Opportunities in Psychiatry

Charter Professional Services, an affiliation of Partners Healthcare System of Boston and the North Shore Medical Center, is recruiting for several psychiatrists. This growing Psychiatry Department has several excellent positions available for the right candidate: Medical Director of an Adult Inpatient Unit of 26 beds; Child Psychiatrist for a 20 bed unit; and Geri Psychiatrist for a 17 bed unit. Some positions have NO WEEKEND call responsibilities!!! You will be part of a dynamic team with a Chair of Psychiatry overseeing all three divisions. This prestigious group is noted for its quality of care and reputation within the community. You will also understand the benefits of a collegial and supportive group practice. Comprehensive benefits and competitive compensation. Salem - North of Boston - is located approximately 12 miles north of the greater Boston area - less than 30 minutes away. Close to all that Boston has to offer: culture, the arts, renowned colleges and universities, outdoor recreation, and great seafood. Excellent school systems and a great place to raise a family. A great place to live, work, and enjoy!

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Or request an application packet at: 701 Ocean St., Room 310, Santa Cruz, CA 95060 (831) 454-2600 • TDD# (831) 454-2123 Equal Opportunity Employer

Endowed Research Professorship in Alzheimer Disease Research Indiana University School of Medicine Department of Psychiatry

The Department of Psychiatry at the Indiana University School of Medicine is seeking qualified applicants for a new endowed research professorship in Alzheimer Disease Research. Essential qualifications include a record of excellence in patient-oriented and/or neurobiological investigation, value placed on education/teaching, mentoring skills, external funding to support research activities, as well as exceptional organizational and interpersonal skills. Preferred candidates will possess a strong background in geriatric psychiatry or related fields and a history of research in Alzheimer Disease and/or other forms of dementia. Candidates must hold an M.D., Ph.D. or combined M.D.-Ph.D. degree, and be eligible for appointment at the rank of Associate or Full Professor.

The Department of Psychiatry currently has strong research programs related to dementia/aging in the areas of epidemiology, mild cognitive impairment, and basic research in gene expression, neurodegeneration, neuroprotection and drug development. The Department has many collaborative research projects, in addition to strong interdisciplinary programs across its clinical and training service missions, with the Division of Geriatric Medicine, and the Departments of Neurology, Pathology and Radiology.

Applications are encouraged from professionals of all ethnic backgrounds. Interested applicants should send their curriculum vita with a summary of relevant clinical/laboratory and academic experience and the names of at least three references to: Christopher J. McDougle, M.D., Albert E. Sterne Professor and Chairman, Department of Psychiatry, Indiana University School of Medicine, 1111 West 10th Street, PB A305, Indianapolis, IN 46202-4800. cmcdougl@iupui.edu.

Applications will be accepted until the position is filled. The departmental website is located at http://www.iupui.edu/~psych/. Indiana University is an EEO/AA Employer, M/F/D.

South Texas Veterans Health Care System

The South Texas Veterans Health Care System (STVHCS) serves one of the largest primary service areas in the nation. STVHCS is comprised of three divisions and has an annual operating budget of \$460 million. San Antonio is surrounded by beautiful Texas hill-country and offers an exceptional suburban lifestyle, excellent schools, and the festive atmosphere of an international city.

Opportunity: Associate Chief of Staff, Mental Health

Location: San Antonio

Job Description: Oversight responsibility for mental health operations for STVHCS, including strategic planning, establishment of policies and procedures, and performance monitoring.

Opportunity: Board-certified or board-eligible Psychiatrists

Location: San Antonio and other South Texas locations

Job Description: Provide treatment to an adult psychiatric population with diverse diagnoses including major affective disorders, psychotic disorders, PTSD, and substance use disorders.

Selected Benefits: Competitive compensation package

Education debt reduction program Eligibility for relocation incentive

Eligibility for academic appointment in the Department of Psychiatry at the University of Texas Health Science Center at

San Antonio

Contact: Mr. Enrique Salas

Human Resources Specialist 210.617.5300 x14952 Enrique.Salas@va.gov

McLeod Regional Medical Center

A 453 bed, tertiary care and teaching facility, located in Florence, South Carolina is recruiting a full-time BC/BE Adult Psychiatrist. Offering a competitive salary guarantee and comprehensive benefits package to include paid professional liability Insurance, CME, and relocation assistance. Call 1/4. Inpatient/outpatient practice setting. 23 bed in-patient unit. Extensive support staff for hospital and ED consults.

The urban population of Florence is 70,000 with 130,000 in the county. Located 2 hours from historic Charleston, and 1 hour from the beach. Recent acknowledgements from Health Grades and the American Hospital Association have identified us as one of the top healthcare systems in the nation for our commitment to quality care and patient safety.

If you're interested in joining this nationally recognized hospital, please contact Tiffany Ellington @ 843-777-5169 or email tellington@mcleodhealth. org.

Top 100 Hospital expanding in Central Texas



Associate Chair Department of Psychiatry

Scott & White and Texas A&M HSC COM seek a Clinical/Academic psychiatrist to lead, manage, and expand an established clinical department as the Associate Chair of the Department of Psychiatry. Candidates should be recognized leaders in psychiatry with demonstrated superior clinical, administrative, and academic skills. The department is playing a critical role as Scott and White increases both its clinical services and academic and research programs. Scott & White is experiencing rapid programmatic growth, and is currently in the process of a \$250 million capital expansion to better meet the needs of our enlarging service area. Academic appointment is commensurate with experience and qualifications through Texas A&M University HSC COM, which is likewise expanding its clinical campuses in Temple and Round Rock.

Scott & White Clinic, a multi-specialty group practice with 550+ physicians, is part of the Scott & White integrated healthcare system which includes Scott & White Memorial Hospital, a 500+ bed tertiary referral center, fourteen supporting regional clinics, and a 180,000 member Scott & White Health Plan (HMO). Temple (with a surrounding population of over 100,000) is centrally located 1 hour north of Austin and an easy drive to the surrounding major metro areas of Dallas-Ft. Worth, Houston and San Antonio.

Scott & White offers a competitive incentive-based salary and comprehensive benefit package, which begins with four weeks vacation, three weeks CME and a generous retirement plan. For additional information, please contact: Kathryn J. Kotrla M.D., Chair, Department of Psychiatry; c/o Jason Culp, Physician Recruiter, Scott & White Clinic, 2401 S. 31st, Temple, TX 76508. (800) 725-3627 jculp@swmail.sw.org Scott & White is an equal opportunity employer. For more information on Scott & White, please visit our web site at: www.sw.org, and for more information about the Texas A&M HSC COM, please visit our web site at: www.tamhsc.edu.







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PSYCHIATRIST (Mental Health Program Manager Position)

The VA Heart of Texas Health Care Network, Arlington, Texas is actively recruiting for a Board Certified Psychiatrist to serve as a Mental Health Program Manager, coordinating and planning mental health care throughout the Network, including ten medical centers and thirty-two Community Based Outpatient Clinics. The medical centers range from smaller, rural facilities to highly affiliated, tertiary care institutions. The Mental Health Program Manager is responsible for final decisions based on Department of Veterans Affairs policy, laws and regulations that govern mental health treatment practice, which directly and substantially affect the Mental Health Program, its facilities and related programs.

The duty station may be located at the Network Office, Arlington, TX; VA North Texas Health Care System, Dallas, TX; Central Texas Veterans Health Care System, Temple, TX; or South Texas Veterans Health Care System, San Antonio, TX.

Relocation expenses and a recruitment bonus are authorized.

The VA offers excellent benefits in a professional and rewarding environment, including 26 vacation days per year, 13 sick leave days per year/accumulates without limit, 10 paid holidays, generous retirement package including 401K savings plan with employer matching contributions, malpractice insurance paid by VA, Education Loan Repayment, and health and life insurance.

Candidates should forward their Curriculum Vitae, statement of professional goals and three references to:

Al Richard - Physician Recruiter (05) • 4500 S. Lancaster Road • Dallas, TX 75216 • AlcintiaD.Richard@va.gov or (214) 857-1685

VA NORTH TEXAS HEALTH CARE SYSTEM

4500 S. Lancaster Road | Dallas, TX 75216 | Located on the Dart Rail Line U.S. Citizenship Required. Applicants Subject to Drug Testing.

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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 trial, modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1 for 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 (a.g., heart failure, sudden death) or intectious (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 acute interest.

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 OT interval cannot be excluded. Therefore, GEODON should not be given with dofetlide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloguine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetror photococy, spantococy, microscocy, monococy, monococy, policy and the most active to the control of the monococy and the mono (see WARNINGS). GEOLOW'S Contrandicated in notwouss with a known hypersensitivity to the product. WARNINGS—increased Mortality in Elderly Patients with Dementia-Related Psychosis: Ederly patients with dementia-Related psychosis treaded 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 Protongation and Risk of Sudden Death*: GEODON use should be avoided in combination with other drugs that are known to protoning the QT, interval. Additionally, clinicians should be alter to the identification of other drugs that have been consistently observed to protoning the QT, interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT,T,T-protoning refer 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 30 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, queltajoine, and halopperidol), 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 OT; 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, 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; 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; prolongations may also increase risk, or increase it in assexplible individuals, such as those with pokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON nypomagnesemia, or generic preusiposision. Animougn or sace de pointer as not open do server un association with me use of tactury at recommended doses in premarketing studies, experience is too limited to rule orta in increase it is.4s. A study evaluating the OT/QT, prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, EC6s 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, 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, from baseline for GEODON was 4.6 mise following the first interval of the properties the first injection and 12.8 msec following the second injection. The mean increase in QT, 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, interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients that offer for the commended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsycholic 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, 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 lorsade de pointes and/or sudden death in association with the use of drugs that prolong the OT, interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the OT, interval; and (4) presence of congenital prolong the OT interval. GEODON should also be avoided in patients with congenital long OT syndrome and in patients with a prolongation of the Liu interval. Lectubus should also be avoided in plateits with congeniant oning Li syndrome and in plateits with history of cardiac arrhythmias (spec CONTRAINDICATIONS, and see Drug Interactions under PRECATIONS). 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 To 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 OT, intervals may also increase the risk of further protongation and arrhythmia, but it is not clear that routine screening EGE 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 OT; 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 or antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation or 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 and recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient requires entity 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 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. Alphyerglycemia and Diabetes Mellitas: Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with alypical 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 abplical antipsychotic should be monitored for symptoms of thy perglycemia. PRECAUTIONS—General: Basis: 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 for 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 c_-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients, GEODON should be used with particular caution in a dienties with known cardiovascular disease, bast failugil infarction or icchemic heart disease, heart failugiles and the properties. aurenergic arriagonist properties. Syncope was reported in 10 % or 15-00 vibro patients, GEDUON should be tased with particular claudion 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 GEODOM patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODOM 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 morbidly 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). <u>Hyperprolactinemia</u>: As with other drugs that antagonize dopamine D, 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 vitro previously detection. 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 nation and the potential forms as 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. <u>Prainsym</u> Ones op fraipsim was reported in the premarketing database. <u>Body Temperature Regulation</u>, 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 Descriptions with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic lineses 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_E prolongation and

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 started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent OT_t 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) lower in the primary Criss effects of decrotors, calcular should be used when it is asken in comination with other extensions acting drugs, (3) Because of its potential for including hypotension, ECDDON may ahnace the effects of certain antihypotension, expensions, (4) GEODON may antagonize the effects of levodopa and dopamine agonists. <u>Effect of Other Drugs on GEODON</u>: <u>Carbamazepine</u>, 200 mg bid for 21 days, resulted in a decrease of lapproximately 35% in the AUC of GEODON. <u>Reboonaze</u>, a potent inhibitor of CYP344, 400 mg df or 5 days, increased the AUC and C_{max} of GEODON by a boat 35%-40%. <u>Cimetidine</u>, 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with bearchords of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with bearchords. oustailephrenic patients in controlled crimical trains has not revealed any still micral pharmacokinetic micral actions with relations propriated for Orazepam. Effect of GEODON on Other Drugs; in Notro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2C9, and CYP3A4, and little potential for drug interactions with GEODON doe to displacement. GEODON 40 mg bild administered concomitantly with *Whitam* 450 mg bild for 7 days did not affect the stead state level or renal clearance of lithium. GEODON 20 mg bild did not affect the pharmacokinetics of concomitantly administered and confraceptives, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON 4 did not after the metabolism of destromethrophan, a CYP2D6 model substrate, to its major metabolite, destrophan. 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 incidence of prilutary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serving longatin 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 observed in a "initial indicary study in the carcinogenicity study. The relevance for human risk of the findings of protactin-mediated endocrine tumors in rodents is unknown (see <u>Hyperprotactinemia</u>). <u>Mutagenesis:</u> 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 in one stain or s. typinarumannia min easistice of metadovic activation. Province testils were obtained in foot in the in vitro chromosomal aberration assay in human lymphocytes. Imparment 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/dy (0,5 to 8 times the MRHD bot 200 mg/kg/dy on a mg/m² basis). Fertility rate was reduced at 160 mg/kg/dy (8 times the MRHD only m² basis). There was no effect on fertility at 40 mg/kg/dy (2 times the MRHD on a mg/m² basis). The fertility of female rats was reduced. *Pregnancy—*Pregnancy-Aregony Category C. There are no adequate and well-controlled studies in pregnant women. GEODON botto do be used during pregnant only if the potential benefit justifies the potential risk to the fetus. Labor and Delivery: The reflect of GEODON on labor and delivery in humans is unknown. *Mursing Mothers: It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human fulls its percommended that women receiving GEODON botto should not be set feet. *Pasterio Iss.* The safety and effectiveness of GEODON in the control of the support of the province of the support of the province of the support of the sup 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 22-74 (19) Where objects or logical order in Ingleteal, inter was fortuitation and understudently for Uctory of the office 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 of the control of the contro Slower tirration, and careful monitoring outing the initial operator is of monitoring the monitoring them the monitoring the monitoring the monitoring them the monitoring Applyonances of San (2012) of the Confirmation and the san frame of the confirmation of the san framework of the san deverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the EGDOON-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 25% 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 events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), diztome (16%), aladmisk (10%), abnormal vision (6%), ashenia (6%), and womiting (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: <u>Body as a Whole</u>—asthenia, accidental injury, chest pain. <u>Cardiovascular</u>—tactycardia. <u>Digestive</u>—nausea, constipation, dyspepsia, diarrhea, drymouth, anorexia. <u>Nervous</u>—extrapyramidal symptoms, somnolence, akathisia, dizziness. <u>Respiratory</u>—respiratory tract infection, rhinitis, cough increased. <u>Skin and Appendages</u>—rash, funga dermatitis. <u>Special Senses</u>—abnormal vision. <u>Biogram Amains Body as a Whole</u>—nausea, accidental injury. <u>Cardiovascular</u>—hypertension. <u>Digestive</u>—nausea, diarrhea, drymouth, vomiting, increased salivation, tongue edema dysphagia. <u>Musculoskeletal</u>—myalgia. <u>Nervous</u>—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. <u>Respiratory</u>—pharyngitis, dyspnea. <u>Skin and Appendages</u>—fungal dermatitis. <u>Special Senses</u>—abnormal vision. <u>Dose Dependency</u>: 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, directors, synonyments. mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, sommolence, 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-ngus Raing Scale and the research as Catalesia Scale did not generally show a difference between GEODON and placebo. What Sign Changes: GEODON is associated with orthostatic Scale did not generally show a difference between GEODOM and placebo. Wital Stign Changes: GEODOM is associated with orthostatic hypotension (see PRECAUTION). Weight Again: In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of 27% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODOM patients (10%) vs placebo patients (4%). A median weight gain of 3 kg was observed in GEODOM patients vs 0.0 kg in placebo patients. Weight again was reported as an adverse event in 0.4% or both GEODOM and placebo patients. During long-term therapy with GEODOM, a categorization of patients atbaseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain of 15 body weight in patients there will a low BMI (e.23) compared to normal (23-27) or overweight C27 patients. There was a mean weight gain of 14 kg for patients with a "own Work baseline BMI, 0.0 kg for patients with a "own BMI (e.23) compared to normal (23-27) or overweight C27 patients. There was a mean weight gain of 14 kg for patients with a "own BMI (e.23) compared to normal (23-27) or overweight C28 was a mean weight gain of 14 kg for patients with a "own BMI (e.23) compared to normal (23-27) or overweight C28 was a mean weight gain of 14 kg for patients with a "own BMI (e.23) compared to normal (23-27) or overweight C28 was a mean weight gain of 14 kg for patients with a "own BMI (e.23) compared to normal (23-27) or overweight C28 was a mean weight gain of 14 kg for patients with a "own BMI (e.23) compared to normal (23-27) or overweight C28 was a mean weight gain of 14 kg for patients with a "own BMI (e.23) compared to normal (23-27) or overweight C28 was a was a mean weight gain of 14 kg for patients with a "own BMI (e.23) compared to normal (23-27) or overweight C28 was a 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 1/100 patients; rare venets are those occurring in 1/100 to 1/100 patients; rare venets are those occurring in events and 1/1000 patients. Schizophrenia <u>Body as a Whole — Frequent Adominal pain</u>, flus syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. <u>Cardiovascular</u> syndrome fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothemia, motor vehicle accident. Cardiovascular System.—Frequent achycarda, hypertension, postural hypotension, infrequent bradycardia, angina pectoris, atrial fibrilon, Razer first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. <u>Digestive System.—Frequent</u> anonexia, vomiting, *Infrequent: retal hemorrhage systhagia, tongue edema; *Razer_gum hemorrhage, jaundice, feeal impaction, gamma glutamy transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena *Endocrine.—*Pare: hypothyroidis. hypothyroidism, thyroiditis. Hemic and Lymphatic System.—Infrequent anemia, ecchymosis, leukocytosis, leukopena, ecsinophilia, hymphadenogathy; *Razer thrombocytopenia, hypochromic anemia, hymphocytosis, monocytosis, basophilia, hymphedema, polycythemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypootalemia, *Raze: BUN increased, creatinine increased, hypercholesteremia, hyperchalemia, hypochloremia, hypoothycemia, hypooratemia, hypocotelomia, dulcose tolerance decreased, on Lity hyperchlorestin, hyporatemia, hypocotelomia, hypoothycemia, chyporatemia, hypocotelomia, dulcose tolerance decreased, on Lity hyperchlorestin, hypocatemia, hypocotelomia, hypocotelomia, hypocatemia, hypocatemia, hypocotelomia, and uncose tolerance decreased, on Lity hyperchlorestin, hypocatemia, hypocotelomia, hypocatemia, hypocatemia, hypocatemia, hypocotelomia, and uncose tolerance decreased, on Lity hyperchlorestin, hypocatemia, hypoca aduunimula, lypocalemia, Azie: buvi nicraesed, creanimie increased, ryperipienta, rypocriosesterinia, ryperialemia, rypocriosesterinia, ryperialemia, rypocalemia, hypogdycemia, hypopatremia, hypoportalemia, lypoportalemia, hypogotycemic reaction, hypoportalemia, hyposocialemia, hypogotycemic reaction, hypoportalemia, hypocalemia, hypogotycemic reaction, hypoportalemia, hypocalemia, ataxia, armesia, cogywhedrigidhy, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incordination, neuropathy, Infraquent paraylisis, Pare: mycolonus, nystagmus, torticollis, circumoral paresthesia, opinthonos, reflexes increased, trismus, <u>Respiratory System</u>— Frequent; dyspnea; Infraquent; pneumoria, epistaxis; Rare: hemoplysis, laryngismus. Skin and Appendages—Infrequent: maculopapular rash, urticaria, alopecia, eczema, exfoliative 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 lacitation, 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, flusyndrome, back pain, Edirovasular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, drymouth. Nervous—dizziness, anwiety, insomnia, somnolence, akathisia, agilitation, extrapyramidal syndrome, hyperotic cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—trinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysemenormea, praipsim. DRUG ABUSE AND DEPENDENCE—Controlled Substance Class:
6E0DON 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

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Control acute agitation with

GEODON

for Injection (ziprasidone mesylate)

In schizophrenia. . .

Rapid control* with low EPS1-4

- Low incidence of movement disorders¹⁻⁴
- Smooth transition, with continued improvement, from IM to oral therapy^{3,4}
- May be used concomitantly with benzodiazepines^{2,3,5}
- *In 2 pivotal studies vs control, significance was achieved at the 2-hour primary end point (10 mg study) and at the 4-hour primary end point (20 mg study).



GEODON for Injection is indicated for the treatment of acute agitation in schizophrenic patients for whom treatment with GEODON is appropriate and who need intramuscular antipsychotic medication for rapid control of the agitation.

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.

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. 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, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

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 include the risk of rash, orthostatic hypotension, and seizures. In fixed-dose, pivotal studies, the most commonly observed adverse events associated with the use of GEODON for Injection (incidence \geq 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.