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

BRIEF SUMMARY

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

CONTRAINDICATIONS
None known.

WARNINGS
Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including LUNESTA. Because some of the important adverse effects of LUNESTA appear to be dose-related, it is important to use the lowest possible effective dose, especially in the elderly (see **DOSAGE AND ADMINISTRATION in the Full Prescribing Information**).

A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of sedative/hypnotics. Some of these changes may be characterized by decreased inhibition (e.g., aggressiveness and extroversion that seem out of character), similar to effects produced by alcohol and other CNS depressants. Other reported behavioral changes have included bizarre behavior, agitation, hallucinations, and depersonalization. Amnesia and other neuropsychiatric symptoms may occur unpredictably. In primarily depressed patients, worsening of depression, including suicidal thinking, has been reported in association with the use of sedative/hypnotics.

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above are drug-induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

Following rapid dose decrease or abrupt discontinuation of the use of sedative/hypnotics, there have been reports of signs and symptoms similar to those associated with withdrawal from other CNS-depressant drugs (see **DRUG ABUSE AND DEPENDENCE**).

LUNESTA, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, LUNESTA should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (e.g., operating machinery or driving a motor vehicle) after ingesting the drug, and be cautioned about potential impairment of the performance of such activities on the day following ingestion of LUNESTA. LUNESTA, like other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression. LUNESTA should not be taken with alcohol. Dose adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents, because of the potentially additive effects.

PRECAUTIONS
General

Timing Of Drug Administration: LUNESTA should be taken immediately before bedtime. Taking a sedative/hypnotic while still up and about may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and lightheadedness.

Use In The Elderly And/Or Debilitated Patients: Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. The recommended starting dose of LUNESTA for these patients is 1 mg (see **DOSAGE AND ADMINISTRATION in the Full Prescribing Information**).

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

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

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

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

Use In Patients With Depression: Sedative/hypnotic drugs should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the least amount of drug that is feasible should be prescribed for the patient at any one time.

Information For Patients: Patient information is printed in the complete prescribing information.

Laboratory Tests: There are no specific laboratory tests recommended.

Drug Interactions

CNS-Active Drugs

Ethanol: An additive effect on psychomotor performance was seen with coadministration of eszopiclone and ethanol 0.70 g/kg for up to 4 hours after ethanol administration.

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

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

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

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

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

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

Drugs With A Narrow Therapeutic Index

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS
The premarketing development program for LUNESTA included eszopiclone exposures in patients and/or normal subjects from two different groups of studies: approximately 400 normal subjects in clinical pharmacology/pharmacokinetic studies, and approximately 1550 patients in placebo-controlled clinical effectiveness studies, corresponding to approximately 263 patient-exposure years. The conditions and duration of treatment with LUNESTA varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, and short-term and longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tabulations that follow, COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while the patient was receiving therapy following baseline evaluation.

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

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

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

*Gender-specific adverse event in females

**Gender-specific adverse event in males

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

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

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

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

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

Adverse events that suggest a dose-response relationship in elderly adults include pain, dry mouth, and unpleasant taste, with this relationship again clearest for unpleasant taste. These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice because patient characteristics and other factors may differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contributions of drug and non-drug factors to the adverse event incidence rate in the population studied.

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

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

Frequent: chest pain, migraine, peripheral edema.

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

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

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

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

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

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

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

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

Signs And Symptoms: Signs and symptoms of overdose effects of CNS depressants can be expected to present as exaggerations of the pharmacological effects noted in preclinical testing. Impairment of consciousness ranging from somnolence to coma has been described. Rare individual instances of fatal outcomes following overdose with racemic zopiclone have been reported in European postmarketing reports, most often associated with overdose with other CNS-depressant agents.

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

Poison Control Center: As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdosage.

Rx only.

SEPRACOR 12/06

Master the Fine Art of Sleep

Prescribe LUNESTA first-line—for a full 7 to 8 hours of sleep

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

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

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

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

Any night or every night

Leave the rest to...

Lunesta® (eszopiclone)C-IV

1, 2 AND 3 MG TABLETS

Important Safety Information

LUNESTA, like other hypnotics, has CNS-depressant effects. Because of the rapid onset of action, LUNESTA should only be ingested immediately prior to going to bed or after the patient has gone to bed and has experienced difficulty falling asleep. Patients should not take LUNESTA unless they are prepared to get a full night's sleep. As with other hypnotics, patients receiving LUNESTA should be cautioned against engaging in hazardous occupations requiring complete mental alertness or motor coordination (eg, operating machinery or driving a motor vehicle) after ingesting the drug, including potential impairment of the performance of such activities that may occur the day following ingestion of LUNESTA. In clinical trials, the most common adverse events associated with LUNESTA were unpleasant taste, headache, somnolence, dizziness, dry mouth, infection, and pain.

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

LUNESTA, like other hypnotics, may produce additive CNS-depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistamines, ethanol, and other drugs that themselves produce CNS depression. LUNESTA should not be taken with alcohol. Dosage adjustment may be necessary when LUNESTA is administered with other CNS-depressant agents because of the potentially additive effects.

Impaired motor and/or cognitive performance after repeated exposure or unusual sensitivity to sedative/hypnotic drugs is a concern in the treatment of elderly and/or debilitated patients. See dosage and administration in complete prescribing information.

Please see brief summary of complete prescribing information.

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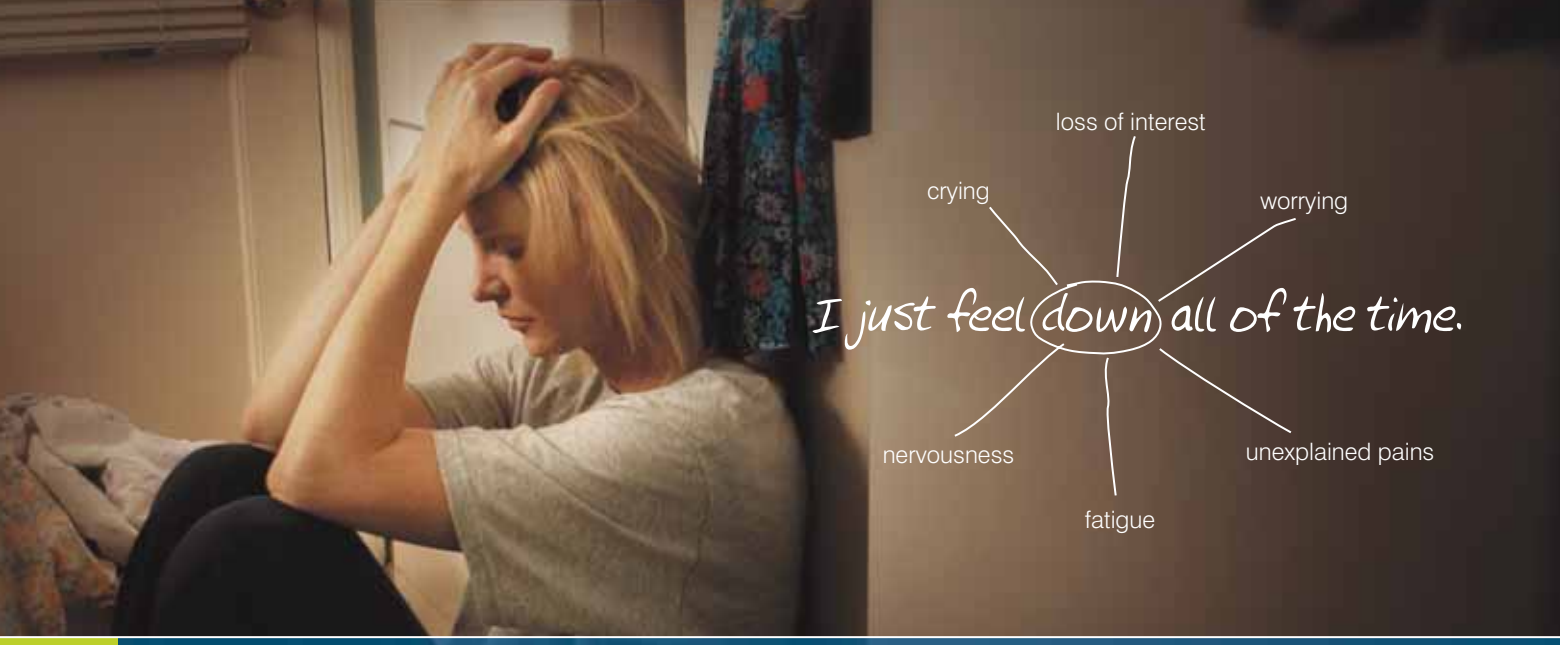

Treat the symptoms of depression your patients talk about, and those they don't. When patients don't express all their symptoms to you, it can make treating depression to remission more complex. Cymbalta is indicated for major depressive disorder (MDD) and treats the emotional, anxious, and painful somatic symptoms of depression.[1a-c,2*] Cymbalta also offers high rates of remission, so patients can feel more like themselves again.[1d†] To learn more about treating beyond the obvious, visit www.insidecymbalta.com

NOW indicated for generalized anxiety disorder (GAD)

* Cymbalta 60 mg/day vs placebo ($P \leq .05$) by MMRM for major depressive disorder (MDD) on mean change in HAM-D_{17} Total Score, Maier Subscale, Psychic Anxiety, and Visual Analog Scale. Full antidepressant response may take 4-6 weeks.

MMRM=Mixed-effects Models Repeated Measures analysis

† Remission=HAM-D_{17} Total Score ≤7, 43% vs 27% placebo, $P \leq .001$, 4 pooled studies.

References: 1. Data on file, Lilly Research Laboratories; a: CYM20060101A; b: CYM20060101B; c: CYM20050315S; d: CYM20060101C.
2. Fava M, et al. *J Clin Psychiatry.* 2004;65(4):521-530.

treat beyond the obvious | Cymbalta® duloxetine HCl DELAYED RELEASE CAPSULES

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 when initiating drug therapy and when increasing or decreasing 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.

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_{1c} 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 adjacent page.

Lilly

CYMBALTA®
(duloxetine hydrochloride) Delayed-release Capsules

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

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 a child, 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 aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with 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-Angle 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.

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 that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. 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 with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), 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 295 short-term trials (median duration of 2 months) of 11 antidepressants drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Drug-Related Increases
<18	14 additional cases
18-24	5 additional cases
	Drug-Related Decreases
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 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. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (*see* PRECAUTIONS, Discontinuation 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, including 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.

MAOIs—In patients receiving a serotonin reuptake inhibitor (SSRI) in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued 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.

Serotonin 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 may 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, 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: ***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) of placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, elevation of ALT > 3 times the upper limit of normal occurred in 1% (39/3732) of Cymbalta-treated patients compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled 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, respectively. Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty 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 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 aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease. Orthostatic Hypotension and Syncope—Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within 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 antihypertensives) or are potent CYP1A2 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 systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg BID. At the highest 200 mg BID dose, the increase in mean pulse rate was 5.0-6.8 bpm and increases in mean blood pressure were 4.7-6.8 mm Hg (systolic) and 4.5-7 mm Hg (diastolic) up to 12 hours after dosing. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes). Activation of Mania/Hypomania—In placebo-controlled trials in patients with MDD, activation of mania or hypomania was reported in 0.1% (2/2327) of duloxetine-treated patients and 0.1% (1/1460) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP or GAD placebo-controlled trials. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of MDD. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania. Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.04% (3/8504) of patients treated with duloxetine and 0.02% (1/6123) of placebo-treated patients. Cymbalta should be prescribed with care in patients with a history of a seizure disorder. Hyponatremia—Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported and appeared to be reversible when Cymbalta was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted. Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma (*see* CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma). Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt discontinuation in placebo-controlled clinical trials, the following symptoms 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: 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 spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, 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 dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

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 motility 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 conditions that may slow gastric emptying (eg, some diabetics). Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta and by 0.2% in the routine care groups. Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis). For this reason, Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients.

Laboratory Tests—No specific laboratory tests are recommended.

Drug Interactions—*Potential for Other Drugs to Affect Cymbalta*—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism. Inhibitors of CYP1A2—Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5-fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided. Inhibitors of CYP2D6—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (eg, fluoxetine, quinidine). *Potential for Duloxetine to Affect Other Drugs*—Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates. Drugs Metabolized by CYP2D6—Cymbalta is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, co-administration of Cymbalta with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C antiarrhythmics (eg, propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered. Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity.

Cymbalta May Have a Clinically Important Interaction with the Following Other Drugs—Alcohol—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol. In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen (*see* PRECAUTIONS, Hepatotoxicity). CNS-Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action. Serotonergic Drugs—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta and the potential for serotonin syndrome, caution is advised when Cymbalta is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (*see* WARNINGS,

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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 tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (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 famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Monoamine Oxidase Inhibitors—*See* CONTRAINDICATIONS *and* WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 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/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis). In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors. Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*. Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at daily doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

Pregnancy—Pregnancy Category C—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development. When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rats; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and =1 times the human dose of 120 mg/day on a mg/m^2 basis in rats; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits). When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

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), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (*see* WARNINGS, Monoamine 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, 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.

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 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 180 days and 445 Cymbalta-treated patients were exposed for at least 1 year. Cymbalta has also been evaluated for safety in 1074 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 daily in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had 12 months of exposure.

Cymbalta has also been evaluated for safety in 668 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 duloxetine and 6123 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 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.

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 not 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. Nausea (Cymbalta 1.4%, placebo 0.1%) 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 of at least twice that of placebo). Diabetic Peripheral Neuropathic Pain—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%), dizziness (Cymbalta 1.6%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0%) and fatigue (Cymbalta 1.1%, placebo 0%) were 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). Generalized Anxiety Disorder—Approximately 16% of the 668 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%) were 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).

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: Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, vomiting; Metabolism and Nutrition Disorders—appetite decreased (includes anorexia); Investigations—weight decreased; General Disorders and Administration Site Conditions—fatigue; Nervous System Disorders—dizziness, somnolence, tremors; Skin and Subcutaneous Tissue Disorders—sweating increased; Vascular Disorders—hot flushes; Eye Disorders—vision blurred; Psychiatric Disorders—insomnia (includes middle insomnia), anxiety, libido decreased, orgasm abnormal (includes anorgasmia); Reproductive System and Breast Disorders—males only: erectile dysfunction, ejaculation delayed, ejaculatory dysfunction (includes ejaculation disorder and 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.

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 QD; N=115 Cymbalta 20 mg QD; N=223 placebo) with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, constipation, diarrhea, dry mouth, vomiting, dyspepsia, loose stools; General Disorders and Administration Site Conditions—fatigue, asthenia, pyrexia; Infections and Infestations—nasopharyngitis; Metabolism and Nutrition Disorders—decreased appetite, anorexia; Musculoskeletal and Connective Tissue Disorders—muscle cramp, myalgia; Nervous System Disorders—somnolence, headache, dizziness, tremor; Psychiatric Disorders—insomnia; Renal and Urinary Disorders—pollakiuria; Reproductive System and Breast Disorders—erectile dysfunction; Respiratory, Thoracic and Mediastinal Disorders—cough, pharyngolaryngeal pain; Skin and Subcutaneous Tissue Disorders—hyperhidrosis.

The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had an incidence ≤ placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth; hyperhidrosis; decreased appetite; and asthenia.

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 60-120 mg once daily) (N=668 Cymbalta; N=495 placebo) and with an incidence greater than placebo were: Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, vomiting, abdominal pain, dyspepsia; General Disorders and Administration Site Conditions—fatigue; Metabolism and Nutrition Disorders—appetite decreased; Nervous System Disorders—dizziness, somnolence, tremor, paraesthesia; Psychiatric Disorders—insomnia, libido decreased, agitation, orgasm abnormal; Reproductive System and Breast Disorders—ejaculation delayed, erectile dysfunction; Respiratory, Thoracic and Mediastinal Disorders—yawning; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—hot 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).

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 Caucasian patients.

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 severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. 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 Item 4) than males treated with placebo. Females did not experience more sexual 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 PI 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. ***Laboratory 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 analytes in Cymbalta-treated patients when compared with placebo-treated patients (*see* PRECAUTIONS). ***Vital Sign 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, 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 of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. ***Electrocardiogram Changes***—Electrocardiograms were obtained from duloxetine-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 fatal. However, in postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but 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 May 15, 2007

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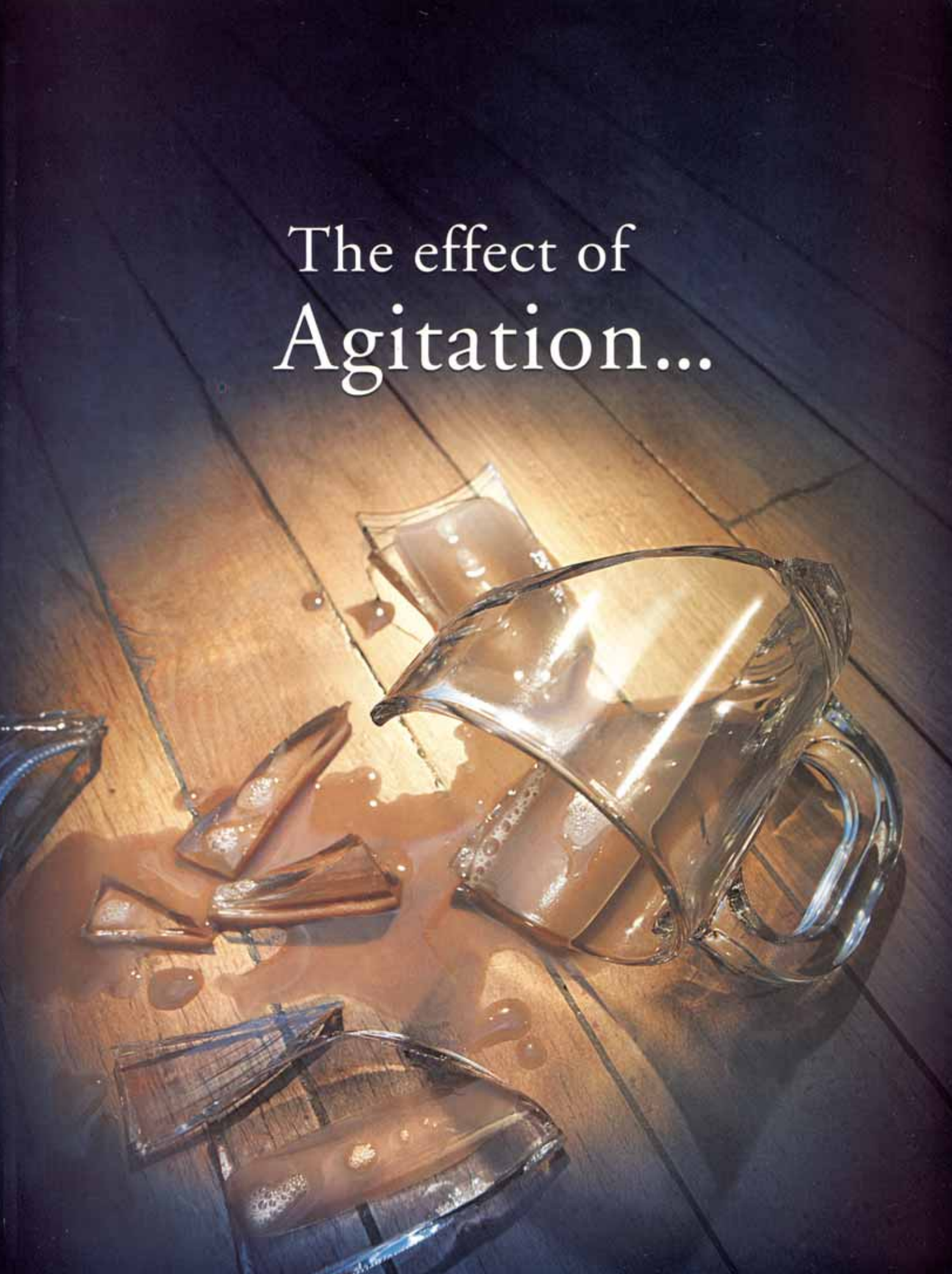
www.Cymbalta.com

Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules PV 5903 AMP

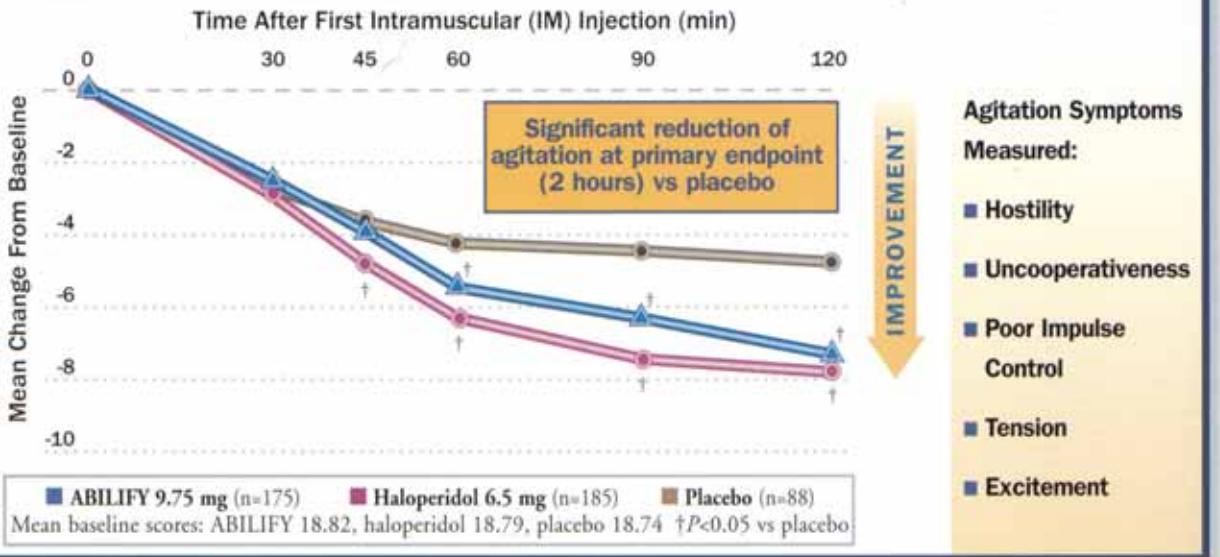

The effect of
Agitation...


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

In schizophrenia or bipolar mania

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

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



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

*Last observation carried forward.

See study description on next page.

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

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

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

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

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

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

ABILIFY® (aripiprazole)
INJECTION 9.75 mg/1.3 mL

HELP ILLUMINATE THE PERSON WITHIN

IMPORTANT SAFETY INFORMATION for ABILIFY® (aripiprazole)

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

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

Treatment-emergent adverse events reported with:

ABILIFY Oral

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

ABILIFY Injection

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

ABILIFY®(aripiprazole) offers your patients:

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

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

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

Study Description:

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

Reference:

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

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

Bristol-Myers Squibb Otsuka America Pharmaceutical, Inc.

570US07AB00102 February 2007 AP444870/02-07 Printed in USA Printed on recycled paper.

ABILIFY® (aripiprazole) TABLETS
ABILIFY® (aripiprazole) ORAL SOLUTION
ABILIFY® DISCMELT™ (aripiprazole) Orally Disintegrating Tablets
ABILIFY® (aripiprazole) INJECTION FOR INTRAMUSCULAR USE ONLY

Rx only

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

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

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

CONTRAINDICATIONS: Known hypersensitivity to aripiprazole

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

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

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

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

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

PRECAUTIONS: General:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

Other Adverse Events Observed During the Premarketing Evaluation of Oral Aripiprazole

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

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole Injection

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

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

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

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

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

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

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
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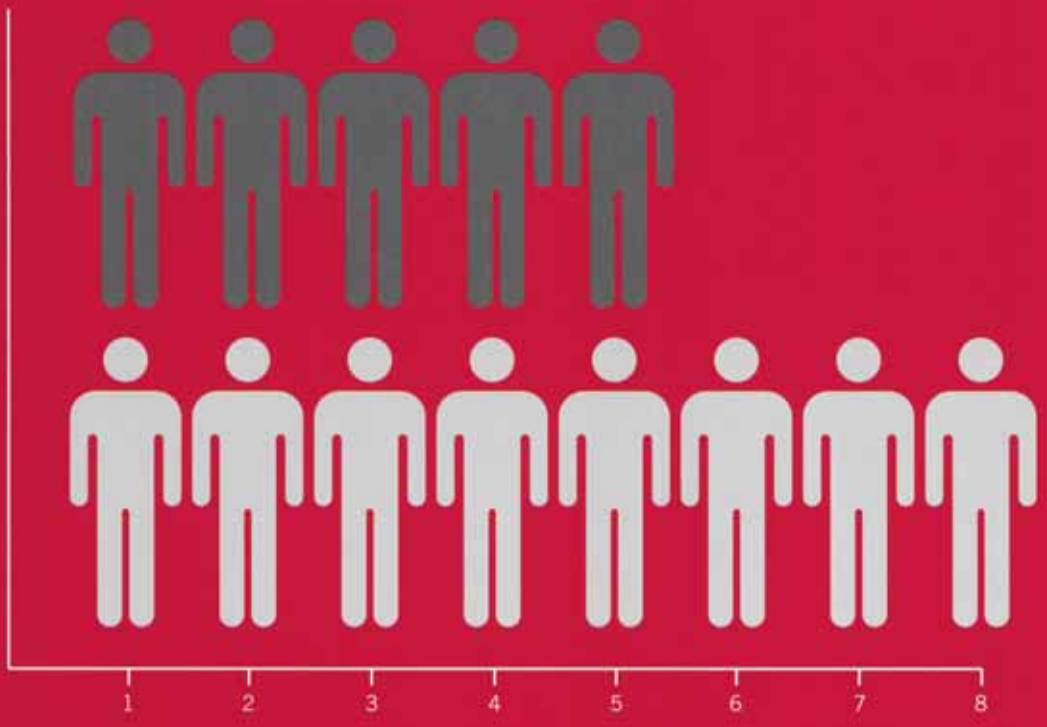


People with severe mental illness die up to 3 decades earlier, on average, than the general population.[1,2]

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

Pfizer

KNOWTHEFACTS

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

Major risk factors include[3]

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

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

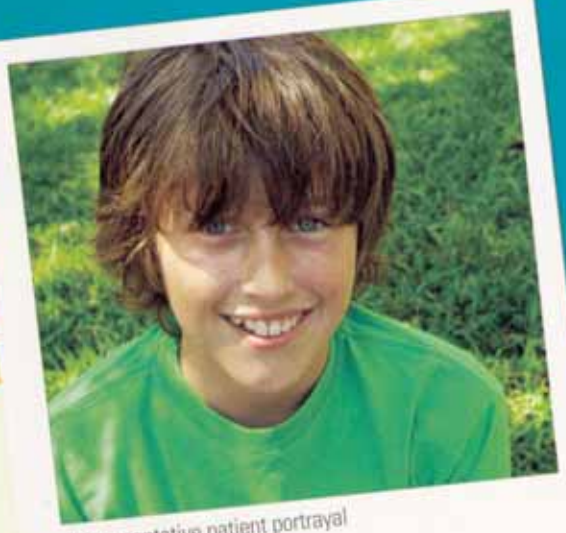
References: 1. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis* [serial online]. 2006 April;3(2). Available at: http://www.cdc.gov/pcd/issues/2006/apr/05_0180.htm.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

GZ279361

Printed in USA/April 2007

For the treatment of attention deficit hyperactivity disorder (ADHD)

CONCERTA® CAN MAKE A DIFFERENCE



Representative patient portrayal

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

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

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

Consider CONCERTA® to give Matthew the help he needs

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

Important Safety Information

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

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

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

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

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

ONCE-DAILY

CONCERTA®

methylphenidate HCl

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

Delivering results that matter

CON07-034

Expires 6/08

CONCERTA® ℞

(methylphenidate HCl) Extended-release Tablets

BRIEF SUMMARY: Please see full prescribing information.

DESCRIPTION

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

CONTRAINDICATIONS

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

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

Glaucoma: CONCERTA® is contraindicated in patients with glaucoma.

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

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

WARNINGS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DRUG DEPENDENCE

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

PRECAUTIONS

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

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

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

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

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

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

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

ADVERSE REACTIONS

The development program for CONCERTA® included exposures in a total of 2121 participants in clinical trials (1787 patients, 324 healthy adult subjects). These participants received CONCERTA® 18, 36, 54, and/or 72 mg/day. Children, adolescents, and adults with ADHD were evaluated in four controlled clinical studies, three open-label clinical studies and two clinical pharmacology studies. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, COSTART terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

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

Treatment-Emergent Adverse Events Among CONCERTA®-Treated Patients: Table 1 enumerates, for a 4-week placebo-controlled, parallel-group trial (Study 3) in children with ADHD at CONCERTA® doses of 18, 36, or 54 mg/day, the incidence of treatment-emergent adverse events. The table includes only those events that occurred in 1% or more of patients treated with CONCERTA® where the incidence in patients treated with CONCERTA® was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1
Incidence of Treatment-Emergent Events' in a 4-Week Placebo-Controlled Clinical Trial of CONCERTA® in Children

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

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

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

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

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

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

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

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

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

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

DRUG ABUSE AND DEPENDENCE

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

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

OVERDOSAGE

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

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

Poison Control Center: As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

Rx Only.

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

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

An ALZA OROS® Technology Product

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Edition: June 2006

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

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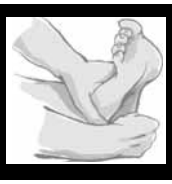

PSYCHIATRY
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CLINICAL NEUROLOGY FOR PSYCHIATRISTS
David Myland Kaufman, MD

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

AMA Statement: Albert Einstein College of Medicine designates this educational activity for a maximum of 25 *AMA PRA Category 1 Credit(s).™* Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

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

PSYCHIATRY FOR PSYCHIATRISTS
Andrea J. Weiss, MD and David Myland Kaufman, MD

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

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City University of New York (CUNY)
Monday, October 8 to Tuesday, October 9, 2007
8:15 AM – 5:15 PM

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

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

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AN ORAL ATYPICAL ANTIPSYCHOTIC FOR THE TREATMENT OF SCHIZOPHRENIA

INVEGA™ PALIPERIDONE

Extended-Release Tablets

IMPORTANT SAFETY INFORMATION FOR INVEGA™ AND RISPERDAL®

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Neither INVEGA™ (paliperidone) nor RISPERDAL® (risperidone) are 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: **INVEGA**: akathisia and extrapyramidal disorder; **RISPERDAL**: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

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

Neuroleptic malignant syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including INVEGA and RISPERDAL. Clinical manifestations include muscle rigidity, fever, altered mental status and evidence of autonomic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs

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

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Created to combine

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

Shown to deliver

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

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, 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 non-deformable formulations. INVEGA should only be used in patients who are able to swallow the tablet whole.

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

Orthostatic hypotension and Syncope: INVEGA and RISPERDAL can cause orthostatic hypotension and syncope in some patients. Appropriate monitoring of orthostatic vital signs should be considered.

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

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

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

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

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

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

Reference: 1. Data on file. Janssen, L.P., Titusville, NJ.

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

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

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

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

PRECAUTIONS

General: Orthostatic Hypotension and Syncope: Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA™ (3, 6, 9, 12 mg) compared to 0.3% (1/355) of subjects treated with placebo. INVEGA™ should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension. **Seizures:** Like other antipsychotic drugs, INVEGA™ should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. **Hyperprolactinemia:** Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. INVEGA™ and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy. **Potential for Cognitive and Motor Impairment:** Somnolence and sedation were reported in subjects treated with INVEGA™ (see ADVERSE REACTIONS). Antipsychotics, including INVEGA™, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them. **Priapism:** No cases of priapism have been reported in clinical trials with INVEGA™. **Thrombotic Thrombocytopenia Purpura (TTP):** No cases of TTP were observed during clinical studies with paliperidone. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown. **Body Temperature Regulation:** Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA™ to patients who will be experiencing conditions which may contribute to an elevation in core body temperature. **Antiemetic Effect:** An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor. **Use in Patients with Concomitant Illness:** Clinical experience with INVEGA™ in patients with certain concomitant illnesses is limited (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: Hepatic Impairment and Renal Impairment in full PI). Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome. INVEGA™ has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA™, caution should be observed in patients with known cardiovascular disease (see PRECAUTIONS: General: Orthostatic Hypotension and Syncope). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe INVEGA™. **Orthostatic Hypotension:** Patients should be advised that there is risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose. **Interference With Cognitive and Motor Performance:** As INVEGA™ has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that INVEGA™ therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with INVEGA™. **Nursing:** Patients should be advised not to breast-feed an infant if they are taking INVEGA™. **Concomitant Medication:** Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions. **Alcohol:** Patients should be advised to avoid alcohol while taking INVEGA™. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in avoiding overheating and dehydration. **Administration:** Patients should be informed that INVEGA™ should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice something that looks like a tablet in their stool. **Drug Interactions: Potential for INVEGA™ to Affect Other Drugs** – Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties. At therapeutic concentrations, paliperidone did not inhibit P-glycoprotein. Paliperidone is therefore not expected to inhibit P-glycoprotein-mediated transport of other drugs in a clinically relevant manner. Given the primary CNS effects of paliperidone (see ADVERSE REACTIONS), INVEGA™ should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists. Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA™ is administered with other therapeutic agents that have this potential (see PRECAUTIONS: General: Orthostatic Hypotension and Syncope). **Potential for Other Drugs to Affect INVEGA™** – Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies of paliperidone have not been performed. Carcinogenicity studies of risperidone, which is extensively converted to paliperidone in rats, mice, and humans, were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at daily doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. The no-effect dose for these tumors was less than or equal to the maximum recommended human dose of risperidone on a mg/m^2 basis (see risperidone package insert). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D_2 antagonism and hyperprolactinemia. The relevance of these tumor findings in rodents in terms of human risk is unknown (see PRECAUTIONS: General: Hyperprolactinemia). **Mutagenesis:** No evidence of genotoxic potential for paliperidone was found in the Ames reverse mutation test, the mouse lymphoma assay, or the *in vivo* rat micronucleus test. **Impairment of Fertility:** In a study of fertility, the percentage of treated female rats that became pregnant was not affected at oral doses of paliperidone of up to 2.5 mg/kg/day. However, pre- and post-implantation loss was increased, and the number of live embryos was slightly decreased, at 2.5 mg/kg, a dose that also caused slight maternal toxicity. These parameters were not affected at a dose of 0.63 mg/kg, which is half of the maximum recommended human dose on a mg/m^2 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/m^2 basis). In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths were seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m^2 basis (see risperidone package insert). Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms. There are no adequate and well controlled studies of INVEGA™ in pregnant women. INVEGA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of INVEGA™ on labor and delivery in humans is unknown. **Nursing Mothers:** In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving INVEGA™ should not breast-feed infants. **Pediatric Use:** Safety and effectiveness of INVEGA™ in patients < 18 years of age have not been established. **Geriatric Use:** The safety, tolerability, and efficacy of INVEGA™ were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older). In this study, subjects received flexible doses of INVEGA™ (3 to 12 mg once daily). In addition, a small number of subjects 65 years of age and older were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of INVEGA™ (3 to 15 mg once daily, see CLINICAL PHARMACOLOGY: Clinical Trials in full PI). Overall, of the total number of subjects in clinical studies of INVEGA™ (n = 1796), including those who received INVEGA™ or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with moderate to severe renal impairment (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Special Populations: Renal Impairment in full PI), who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION: Dosing in Special Populations in full PI).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for INVEGA™ consisting of 2720 patients and/or normal subjects exposed to one or more doses of INVEGA™ for the treatment of schizophrenia. Of these 2720 patients, 2054 were patients who received INVEGA™ while participating in multiple dose, effectiveness trials. The conditions and duration of treatment with INVEGA™ varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose studies, and short-term and longer-term exposure. Adverse events were assessed by collecting adverse events and performing physical examinations, vital signs, weights, laboratory analyses and ECGs. Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology. The stated frequencies of adverse events represent the proportions of individuals who experienced a treatment-emergent adverse event of the type listed. An event was

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

DRUG ABUSE AND DEPENDENCE

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

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

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Janssen L.P.

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RISPERDAL®
(RISPERIDONE)
TABLETS/ORAL SOLUTION

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

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

Increased Mortality in Elderly Patients with Dementia–Related Psychosis

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

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

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

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

PRECAUTIONS: General: Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL®-treated patients in Phase 2 and 3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in the elderly and patients with renal or hepatic impairment (see DOSAGE AND ADMINISTRATION in full PI). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension, e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication. **Seizures:** RISPERDAL® should be used cautiously in patients with a history of seizures. **Dysphagia:** Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. (See also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis.**) **Hyperprolactinemia:** As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. An increase in pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats (see PRECAUTIONS – Carcinogenesis, Mutagenesis, Impairment of Fertility). Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose-related. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely. **Priapism:** Rare cases of priapism have been reported. **Thrombotic Thrombocytopenic Purpura (TTP):** A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown. **Antiemetic Effect:** Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor. **Body Temperature Regulation:** Disruption of body temperature regulation has been attributed to antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to temperature extremes. **Suicide:** The possibility of a suicide attempt is inherent in patients with schizophrenia and bipolar mania, including children and adolescent patients, and close supervision of high-risk patients should accompany drug therapy. **Use in Patients With Concomitant Illness:** Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL®, are reported to have an increased sensitivity to antipsychotic medications. Manifestations of this increased sensitivity have been reported to include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Increased plasma concentrations of risperidone and 9–hydroxyrisperidone occur in patients with severe renal impairment and in patients with severe hepatic impairment. A lower starting dose should be used in such patients. **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe RISPERDAL®: **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration. **Interference With Cognitive and Motor Performance:** Since RISPERDAL® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Nursing:** Patients should be advised not to breast-feed an infant if they are taking RISPERDAL®. **Concomitant Medication:** Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. **Alcohol:** Patients should be advised to avoid alcohol while taking RISPERDAL®. **Phenylketonurics:** Phenylalanine is a component of aspartame. Each 4 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.84 mg phenylalanine; each 3 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.63 mg

phenylalanine; each 2 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.42 mg phenylalanine; each 1 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.28 mg phenylalanine; and each 0.5 mg RISPERDAL® M-TAB® Orally Disintegrating Tablet contains 0.14 mg phenylalanine. **Drug Interactions:** The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol. Because of its potential for inducing hypotension, RISPERDAL® may enhance the hypotensive effects of other therapeutic agents with this potential. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone. **Carbamazepine and Other Enzyme Inducers:** In a drug interaction study in schizophrenic patients, 11 subjects received risperidone titrated to 6 mg/day for 3 weeks, followed by concurrent administration of carbamazepine for an additional 3 weeks. During co-administration, the plasma concentrations of risperidone and its pharmacologically active metabolite, 9–hydroxyrisperidone, were decreased by about 50%. Plasma concentrations of carbamazepine did not appear to be affected. The dose of risperidone may need to be titrated accordingly for patients receiving carbamazepine, particularly during initiation or discontinuation of carbamazepine therapy. Co-administration of other known enzyme inducers (e.g., phenytoin, rifampin, and phenobarbital) with risperidone may cause similar decreases in the combined plasma concentrations of risperidone and 9–hydroxyrisperidone, which could lead to decreased efficacy of risperidone treatment. **Fluoxetine and Paroxetine:** Fluoxetine (20 mg QD) and paroxetine (20 mg QD) have been shown to increase the plasma concentration of risperidone 2.5-2.8 fold and 3-9 fold respectively. Fluoxetine did not affect the plasma concentration of 9–hydroxyrisperidone. Paroxetine lowered the concentration of 9–hydroxyrisperidone by about 10%. When either concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL®. The effects of discontinuation of concomitant fluoxetine or paroxetine therapy on the pharmacokinetics of risperidone and 9–hydroxyrisperidone have not been studied. **Lithium:** Repeated oral doses of risperidone (3 mg BID) did not affect the exposure (AUC) or peak plasma concentrations (C_{max}) of lithium (n=13). **Valproate:** Repeated oral doses of risperidone (4 mg QD) did not affect the pre-dose or average plasma concentrations and exposure (AUC) of valproate (1000 mg/day in three divided doses) compared to placebo (n=21). However, there was a 20% increase in valproate peak plasma concentration (C_{max}) after concomitant administration of risperidone. **Digoxin:** RISPERDAL® (0.25 mg BID) did not show a clinically relevant effect on the pharmacokinetics of digoxin. **Drugs That Inhibit CYP 2D6 and Other CYP Isozymes:** Risperidone is metabolized to 9–hydroxyrisperidone by CYP 2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (see CLINICAL PHARMACOLOGY in full PI). Drug interactions that reduce the metabolism of risperidone to 9–hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9–hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n=70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made. *In vitro* studies showed that drugs metabolized by other CYP isozymes, including 1A1, 1A2, 2C9, 2C19, and 3A4, are only weak inhibitors of risperidone metabolism. There were no significant interactions between risperidone and erythromycin (see CLINICAL PHARMACOLOGY in full PI). **Drugs Metabolized by CYP 2D6:** *In vitro* studies indicate that risperidone is a relatively weak inhibitor of CYP 2D6. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis:** Carcinogenicity studies were conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4, and 37.5 times the maximum recommended human dose (MRHD) for schizophrenia (16 mg/day) on a mg/kg basis or 0.2, 0.75, and 3 times the MRHD (mice) or 0.4, 1.5, and 6 times the MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas, and mammary gland adenocarcinomas. These findings are considered to be prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS, General - Hyperprolactinemia). **Mutagenesis:** No evidence of mutagenic potential for risperidone was found. **Impairment of Fertility:** Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of risperidone was studied in three Segment II studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one Segment II study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the MRHD on a mg/m^2 basis. In three reproductive studies in rats (two Segment III and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5 mg/kg or 0.1 to 3 times the MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams. There was no no-effect dose for increased rat pup mortality. In one Segment III study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the MRHD on a mg/m^2 basis. In a cross-fostering study in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in the number of live pups and an increase in the number of dead pups at birth (Day 0), and a decrease in birth weight in pups of drug-treated dams were observed. In addition, there was an increase in deaths by Day 1 among pups of drug-treated dams, regardless of whether or not the pups were cross-fostered. Risperidone also appeared to impair maternal behavior in that pup body weight gain and survival (from Day 1 to 4 of lactation) were reduced in pups born to control but reared by drug-treated dams. These effects were all noted at the one dose of risperidone tested, i.e., 5 mg/kg or 3 times the MRHD on a mg/m^2 basis. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of RISPERDAL® on labor and delivery in humans is unknown. **Nursing Mothers:** In animal studies, risperidone and 9–hydroxyrisperidone are excreted in milk. Risperidone and 9–hydroxyrisperidone are also excreted in human breast milk. Therefore, women receiving risperidone should not breast-feed. **Pediatric Use:** The safety and effectiveness of RISPERDAL® in pediatric patients with schizophrenia or bipolar mania have not been established. **Tardive Dyskinesia:** In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, 2 (0.1%) patients were reported to have tardive dyskinesia, which resolved on discontinuation of risperidone treatment (see WARNINGS – Tardive Dyskinesia). **Weight Gain:** In long-term, open-label trials (studies in patients with autistic disorder or other psychiatric disorders), a mean increase of 7.5 kg after 12 months of RISPERDAL® treatment was observed, which was higher than the expected normal weight gain (approximately 3 to 3.5 kg per year adjusted for age, based on Centers for Disease Control and Prevention normative data). The majority of that increase occurred within the first 6 months of exposure to RISPERDAL®. The average percentiles at baseline and 12 months, respectively, were 49 and 60 for weight, 48 and 53 for height, and 50 and 62 for body mass index. When treating patients with RISPERDAL®, weight gain should be assessed against that expected with normal growth. (See also ADVERSE REACTIONS.) **Somnolence:** Somnolence was frequently observed in placebo-controlled clinical trials of pediatric patients with autistic disorder. Most cases were mild or moderate in severity. These events were most often of early onset with peak incidence occurring during the first two weeks of treatment, and transient with a median duration of 16 days. (See also ADVERSE REACTIONS.) Patients experiencing persistent somnolence may benefit from a change in dosing regimen. **Hyperprolactinemia, Growth, and Sexual Maturation:** Risperidone has been shown to elevate prolactin levels in children and adolescents as well as in adults (see PRECAUTIONS - Hyperprolactinemia). In double-blind, placebo-controlled studies of up to 8 weeks duration in children and adolescents (aged 5 to 17 years), 49% of patients who received risperidone had elevated prolactin levels compared to 2% of patients who received placebo. In clinical trials in 1885 children and adolescents with autistic disorder or other psychiatric disorders treated with risperidone, galactorrhea was reported in 0.8% of risperidone-treated patients and gynecomastia was reported in 2.3% of risperidone-treated patients. The long-term effects of risperidone on growth and sexual maturation have not been fully evaluated. **Geriatric Use:** Clinical studies of RISPERDAL® in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and over to determine whether or not they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in full PI). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (see PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. This drug is substantially excreted by the kidneys, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION in full PI). **Concomitant use with Furosemide in Elderly Patients with Dementia-Related Psychosis:** In placebo-controlled trials in elderly patients with dementia-related psychosis, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or with placebo plus furosemide. No pathological mechanism has been identified to explain this finding, and no consistent pattern for cause of death was observed. An increase of mortality in elderly patients with dementia-related psychosis was seen with the use of RISPERDAL® regardless of concomitant use with furosemide. RISPERDAL® is not approved for the treatment of patients with dementia-related psychosis. (See **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**.)

ADVERSE REACTIONS: Associated With Discontinuation of Treatment: Bipolar Mania: In the US placebo-controlled trial with risperidone as monotherapy, approximately 8% (10/134) of RISPERDAL®-treated patients discontinued treatment due to an adverse event, compared with approximately 6% (7/125) of placebo-treated patients. The adverse events associated with discontinuation and considered to be possibly, probably, or very likely drug-related included paroniria, somnolence, dizziness, extrapyramidal disorder, and muscle contractions involuntary. Each of these events occurred in one RISPERDAL®-treated patient (0.7%) and in no placebo-treated patients (0%). In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, there was no overall difference in the incidence of discontinuation due to adverse events (4% for RISPERDAL® vs. 4% for placebo). **Incidence in Controlled Trials: Commonly Observed Adverse Events in Controlled Clinical Trials:** ***Bipolar Mania:*** In the US placebo-controlled trial with risperidone as monotherapy, the most commonly observed adverse events associated with the use of RISPERDAL® (incidence of 5% or greater and at least twice that of placebo) were somnolence, dystonia, akathisia, dyspepsia, nausea, parkinsonism, vision abnormal, and saliva increased. In the US placebo-controlled trial with risperidone as adjunctive therapy to mood stabilizers, the most commonly observed adverse events associated with the use of RISPERDAL® were somnolence, dizziness, parkinsonism, saliva increased, akathisia, abdominal pain, and urinary incontinence. *Adverse Events Occurring at an Incidence of 2% or More Among RISPERDAL®-Treated Patients - Bipolar Mania:* Adverse events that occurred at an incidence of 2% or more, and were more frequent among patients treated with flexible doses of RISPERDAL® (1-6 mg daily as monotherapy and as adjunctive therapy to mood stabilizers, respectively) than among patients treated with placebo. Reported adverse events were classified using the World Health Organization preferred terms. *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial-Monotherapy in Bipolar Mania.* **Body System/Preferred Term: Central & peripheral nervous system:** Dystonia, Akathisia, Dizziness, Parkinsonism, Hypoaesthesia **Psychiatric:** Somnolence, Agitation, Manic reaction, Anxiety, Concentration impaired **Gastrointestinal system:** Dyspepsia, Nausea, Saliva increased, Mouth dry **Body as a whole - general:** Pain, Fatigue, Injury **Respiratory system:** Sinusitis, Rhinitis, Coughing **Skin and appendages:** Acne, Pruritus **Musculo-Skeletal:** Myalgia, Skeletal pain **Metabolic and nutritional:** Weight increase **Vision disorders:** Vision abnormal **Cardiovascular, general:** Hypertension, Hypotension **Heart rate and rhythm:** Tachycardia. *Incidence of Treatment-Emergent Adverse Events in a 3-Week, Placebo-Controlled Trial – Adjunctive Therapy in Bipolar Mania.* **Body System/Preferred Term: Gastrointestinal system:** Saliva increased, Diarrhea, Abdominal pain, Constipation, Mouth dry, Tooth ache, Tooth disorder **Central & peripheral nervous system:** Dizziness, Parkinsonism, Akathisia, Dystonia **Psychiatric:** Somnolence, Anxiety, Confusion **Respiratory system:** Rhinitis, Pharyngitis, Coughing **Body as a whole - general:** Asthenia **Urinary system:** Urinary incontinence **Heart rate and rhythm:** Tachycardia **Metabolic and nutritional:** Weight increase **Skin and appendages:** Rash. **Dose Dependency of Adverse Events:** Data from two fixed-dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment. These symptoms include: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatigability, and increased pigmentation. ***Vital Sign Changes:*** RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS). ***Weight Changes:*** A statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%). ***Laboratory Changes:*** A between-group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (see PRECAUTIONS). ***ECG Changes:*** Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between risperidone and placebo in mean changes from baseline in ECG parameters, including QT, QTc, and PR intervals, and heart rate. When all RISPERDAL® doses were pooled from randomized controlled trials in several indications, there was a mean increase in heart rate of 1 beat per minute compared to no change for placebo patients. In short-term schizophrenia trials, higher doses of risperidone (8-16 mg/day) were associated with a higher mean increase in heart rate compared to placebo (4-6 beats per minute). **Adverse Events and Other Safety Measures in Pediatric Patients With Autistic Disorder:** In the two 8-week, placebo-controlled trials in pediatric patients treated for irritability associated with autistic disorder (n=156), two patients (one treated with RISPERDAL® and one treated with placebo) discontinued treatment due to an adverse event. *Incidence of Treatment-Emergent Adverse Events in Two 8-Week, Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder.* **Body System Preferred Term: Psychiatric:** Somnolence, Appetite increased, Confusion **Gastrointestinal:** Saliva increased, Constipation, Dry mouth **Body as a whole - general:** Fatigue **Central & peripheral nervous system:** Tremor, Dystonia, Dizziness, Automatism, Dyskinesia, Parkinsonism **Respiratory**: Upper respiratory tract infection **Metabolic and nutritional**: Weight increase **Heart rate and rhythm**: Tachycardia **Other Events Observed During the Premarketing Evaluation of RISPERDAL®:** During its premarketing assessment, multiple doses of RISPERDAL® were administered to 2607 adult patients with schizophrenia and 1923 pediatric patients in Phase 2 and 3 studies and the following reactions were reported: (Note: frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it). Serious adverse reactions experienced by the pediatric population were similar to those seen in the adult population (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS). **Psychiatric Disorders:** *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning. **Central and Peripheral Nervous System Disorders:** *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis. **Gastrointestinal Disorders:** *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastroesophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis. **Body as a Whole/General Disorders:** *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing. **Respiratory System Disorders:** *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration. **Skin and Appendage Disorders:** *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria. **Cardiovascular Disorders:** *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis. **Vision Disorders:** *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation. **Metabolic and Nutritional Disorders:** *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia. **Urinary System Disorders:** *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency. **Musculo-Skeletal System Disorders:** *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain. Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage. **Liver and Biliary System Disorders:** *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage. Platelet, Bleeding, and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia. **Hearing and Vestibular Disorders:** *Rare:* tinnitus, hyperacusis, decreased hearing. **Red Blood Cell Disorders:** *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia. **Reproductive Disorders, Male:** *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure. **White Cell and Resistance Disorders:** *Infrequent:* granulocytopenia. *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly. **Endocrine Disorders:** *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder. **Special Senses:** *Rare:* bitter taste.*Incidence based on elicited reports. **Postintroduction Reports:** Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pituitary adenomas, pulmonary embolism, precocious puberty, and QT prolongation. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

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

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Janssen L.P.

01RS1950SB

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

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

WARNING

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 (*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 (eg, 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 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 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. Patients who develop symptoms of hyperglycemia during treatment with atypicals should undergo FBG testing.

Neuroleptic Malignant Syndrome (NMS)—Potentially fatal NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. See complete prescribing information for information on management of NMS. Patients requiring antipsychotic drug treatment after recovery from NMS should be carefully monitored since recurrences have been reported.

Tardive Dyskinesia (TD)—Potentially irreversible TD may develop in patients treated with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are more likely to develop the syndrome. If signs and symptoms of TD appear, consider drug discontinuation.

PRECAUTIONS: Hemodynamic Effects—Olanzapine may induce orthostatic hypotension associated with dizziness; tachycardia; 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). The risk for this 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 drowsy 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). Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is not recommended. If such combination treatment is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Seizures—During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients, regardless of causality. Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

Hyperprolactinemia—Like other drugs that antagonize dopamine D2 receptors, olanzapine elevates prolactin levels; a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro. However, neither clinical nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is inconclusive.

Transaminase Elevations—In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of normal) were observed in 2% (6/243) of patients exposed to olanzapine compared to no (0/115) placebo patients. None of these patients experienced jaundice. Among about 2400 patients with baseline SGPT ≤90 IU/L, 2% (50/2381) had asymptomatic SGPT elevations to >200 IU/L. Most were transient changes that tended to normalize while olanzapine treatment was continued. Among 2500 patients in oral olanzapine trials, about 1% (23/2500) discontinued treatment due to transaminase increases. Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period. Exercise caution in patients who have signs and symptoms of hepatic impairment; preexisting conditions associated with limited hepatic functional reserve; or concomitant treatment with potentially hepatotoxic drugs (*see* Laboratory Tests, below).

Potential for Cognitive and Motor Impairment—Somnolence was a commonly reported, dose-related adverse event in premarketing trials (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 dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's 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 greater than with placebo: falls, somnolence, peripheral edema, abnormal gait, 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 orthostatic hypotension with olanzapine, use caution in cardiac patients (*see* Hemodynamic Effects).

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

Laboratory Tests—Periodic assessment of transaminases is recommended in patients with significant hepatic 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 enzymes (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, 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 cimetidine (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) nor warfarin (20 mg 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 in 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 imipramine/desipramine or warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam/N-desmethyldiazepam, lithium, ethanol, or biperiden. However, coadministration 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/m^2 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/m^2 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 rodents is unknown. No evidence of mutagenic potential for olanzapine has been found.

In rats, fertility (females) and mating performance (males and females) were affected at doses 1.5-11 times the MHDOD (mg/m^2 basis). Diestrous was prolonged and estrous delayed at 0.6 times the MHDOD (mg/m^2 basis); therefore, olanzapine may produce a delay in ovulation.

Pregnancy Category C—There are no adequate and well-controlled studies in pregnant women. Olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery, Nursing Mothers—Parturition in rats was not affected by olanzapine; its effect on labor and delivery in humans is unknown. In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal dose. It is recommended that women receiving olanzapine should not breast-feed.

Use in Pediatric and Geriatric Patients—Safety and effectiveness in pediatric patients have not been established. In premarketing clinical trials in patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested there may be a different tolerability profile in these patients. 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 these patients, vigilance should be exercised. Consider a lower starting dose for any geriatric patient in the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine (*see* BOX WARNING, WARNINGS, *and* PRECAUTIONS).

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 I disorder (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 sign changes, 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 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 alone]); or in placebo-controlled intramuscular olanzapine for injection trials (olanzapine for injection, 0.4%; 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 gain, dizziness, 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 associated with oral olanzapine were: asthenia, dry mouth, constipation, dyspepsia, increased appetite, somnolence, dizziness, and tremor. In short-term bipolar mania combination therapy trials, the most common treatment-emergent adverse events observed with olanzapine plus lithium or valproate were dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, and paresthesia. In 24-hour placebo-controlled trials of intramuscular olanzapine for injection for agitation 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 ≥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, cough increased, pharyngitis; ***Special Senses***—amblyopia; ***Urogenital***—urinary incontinence, urinary tract infection.

Adverse Events with an Incidence ≥2% in Oral Combination Therapy Trials—The following treatment-emergent events were reported at an incidence of ≥2% with oral olanzapine (doses ≥5 mg/d) plus lithium or valproate (N=229), 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, 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/injection) and at incidence greater than placebo in short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania: ***Body 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 scales incidence between any dose of oral olanzapine (5±2.5, 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 akathisia 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

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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 placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

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.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, 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), 56% 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 asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

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 from a mean baseline of 175 mg/dL. In placebo-controlled trials, olanzapine-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, olanzapine-treated patients (N=2528) had a mean increase of 0.4 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.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/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 ≥1 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; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. ***Body as a Whole***—*Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck 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, 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, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. ***Endocrine***—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. ***Hemic and Lymphatic***—*Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. ***Metabolic and Nutritional***—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, 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, 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, stridor. ***Skin and Appendages***—*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, 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. (*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:* AV block, heart block, syncope. ***Digestive***—*Infrequent:* diarrhea, nausea. ***Hemic and Lymphatic***—*Infrequent:* anemia. ***Metabolic and Nutritional***—*Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. ***Musculoskeletal***—*Infrequent:* twitching. ***Nervous System***—*Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. ***Skin and Appendages***—*Infrequent:* sweating.

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.

Literature revised November 30, 2006

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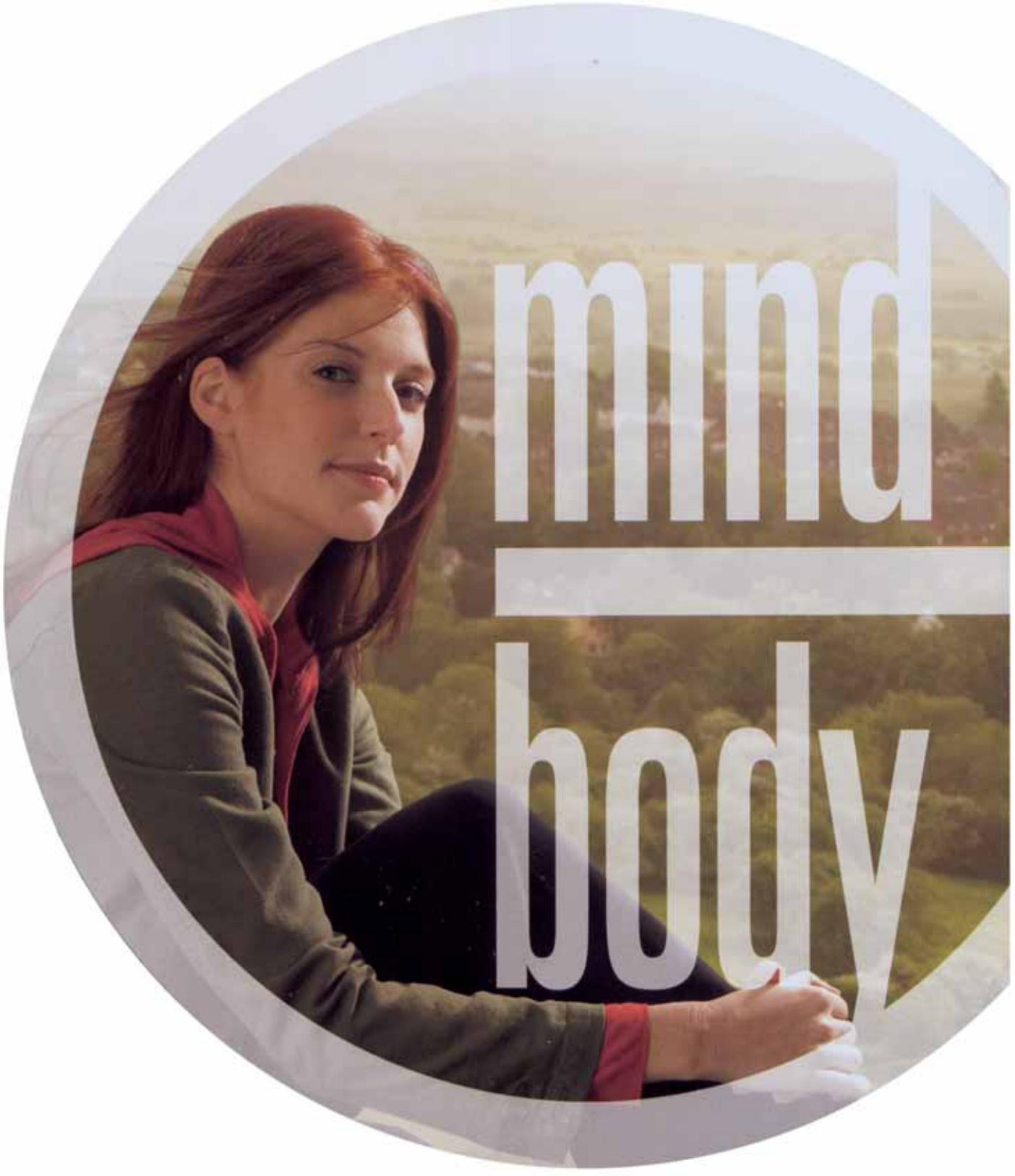
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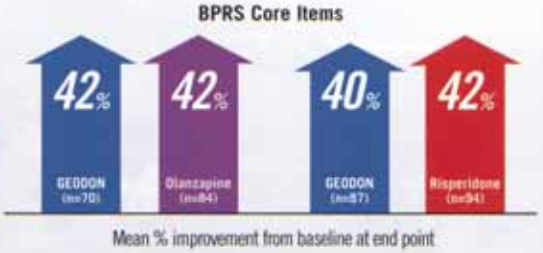
IN SCHIZOPHRENIA

Treat With the Body in Mind

CHOOSE COMPARABLE POWER...

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



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

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

...WITHOUT COMPROMISING METABOLIC PARAMETERS

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

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

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

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

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

GEODON is indicated for the treatment of schizophrenia.

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

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

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

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

Pfizer

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

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

BRIEF SUMMARY. See package insert for full prescribing information.

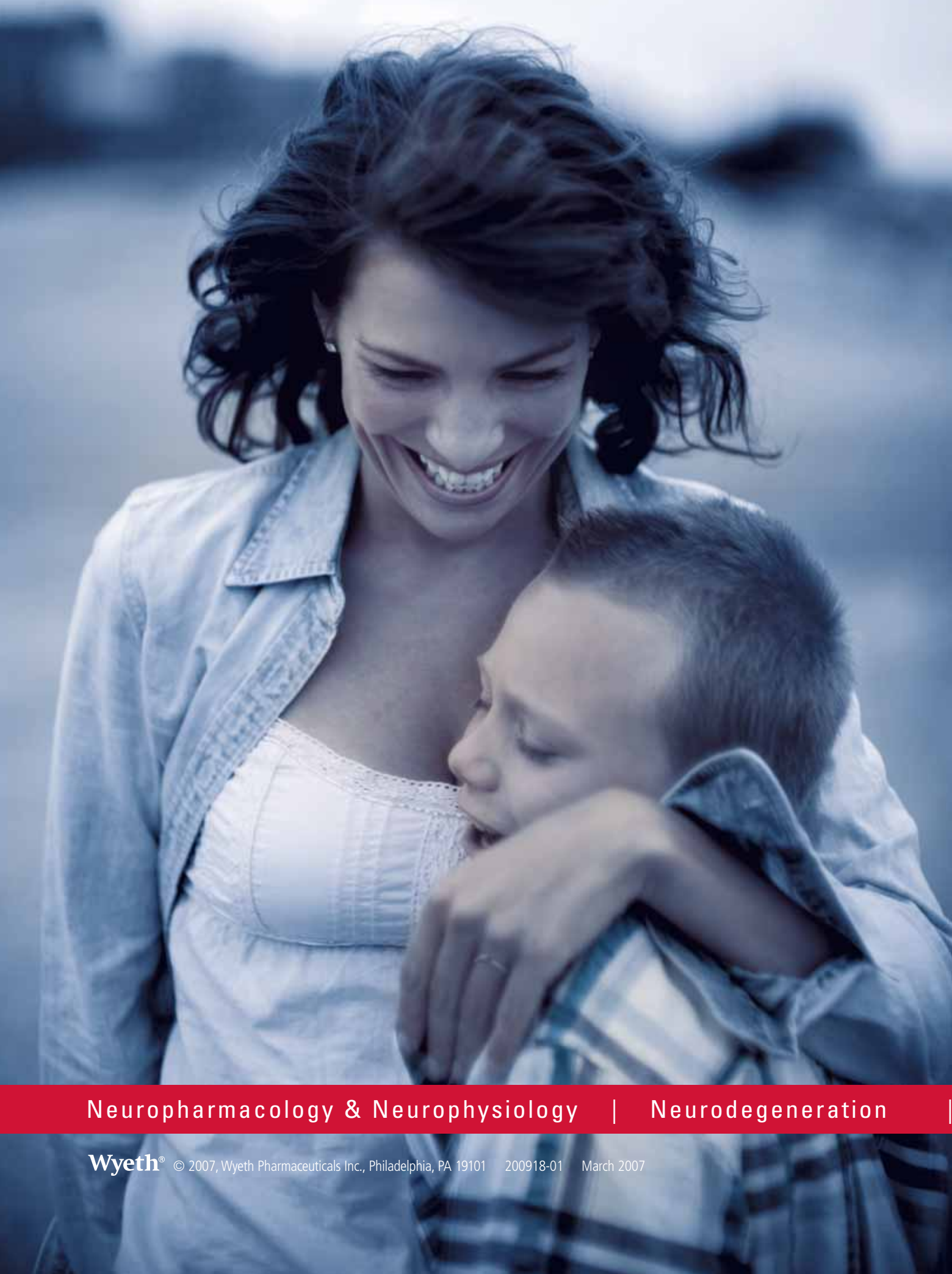
Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these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

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

CONTRAINDICATIONS — *QT Prolongation:* Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS—Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning). *QT Prolongation and Risk of Sudden Death:* GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT_c prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec. *Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS — *General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis).** Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole*, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum zprolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m² basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m² basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m² basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS — *Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Schizophrenia: Body as a Whole—*Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System—*Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System—*Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine—*Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System—*Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders—*Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hyperproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System—*Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System—*Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System—*Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages—*Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses—*Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System—*Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE—*Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/95).

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

Revised November 2006



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It may be time to make a change
* Patients currently on an SSRI should be evaluated following an adequate trial.

IMPORTANT TREATMENT CONSIDERATIONS

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 EFFEXOR XR or any other antidepressant in a child, 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 aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with 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. EFFEXOR XR is not approved for use in pediatric patients. (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use.)

- **EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI; at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.**
- Adult and pediatric patients with MDD can experience worsening of their depression and/or the emergence of suicidal ideation and behavior, whether or not they are taking antidepressants. **All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or

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Break the Cycle

of unresolved depression with EFFEXOR XR

Achieve remission

- In an open-label study of patients who failed previous antidepressant treatment, nearly **60%** achieved remission when changed to EFFEXOR XR[1,2]

Sustain remission

- In the PREVENT™ study, **77%** of EFFEXOR XR patients were in remission at 2 years vs. 48% with placebo[2†]

Go beyond remission: Reduce recurrence

- In the PREVENT™ study, there was an **82%** reduction in the probability of recurrence with EFFEXOR XR in maintenance year 2 vs. placebo[2†]

modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms.

- The development of potentially life-threatening serotonin syndrome may occur when EFFEXOR XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems. Concomitant use of EFFEXOR XR with MAOIs is contraindicated. If concomitant use of EFFEXOR XR with an SSRI, SNRI, or a triptan is clinically warranted, careful observation of the patient is advised. Concomitant use of EFFEXOR XR with tryptophan supplements is not recommended.
- Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.
- Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually. See the Precautions section of the Prescribing Information.
- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled MDD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence ≥10% and ≥2x that of placebo) were anorexia, asthenia, constipation, dizziness, dry mouth, ejaculation problems, impotence, insomnia, nausea, nervousness, somnolence, and sweating.

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

† A randomized, multicenter, double-blind, placebo-controlled study (N=1,096 adults). This trial included an acute, a continuation, and 2 one-year maintenance phases. At the start of each of the 2 maintenance phases, EFFEXOR XR responders were re-randomized to either EFFEXOR XR or placebo. The primary end point was time to recurrence of depression. For study design, please visit **PreventStudy.com**.

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References: 1. Baldomero EB, Ubago JG, Cercós CL, et al. Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. *Depress Anxiety*. 2005;22:68-76. **2.** Data on file, Wyeth Pharmaceuticals Inc.

Please see brief summary of Prescribing Information on adjacent pages.

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BRIEF SUMMARY. See package insert for full prescribing information.

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 EFFEXOR XR or any other antidepressant in a child, 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 aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with 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. EFFEXOR XR is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

CONTRAINDICATIONS: Hypersensitivity to venlafaxine hydrochloride or to any excipients in the formulation. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs). **WARNINGS: Clinical Worsening and Suicide Risk**—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. 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 that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. 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 with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1 of the full prescribing information. 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. However, 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.** Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD and other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**). **Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. **Screening Patients for Bipolar Disorder**: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. Prior to initiating antidepressant treatment, patients with depressive symptoms should be screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. Effexor XR is not approved for use in treating bipolar depression. **Potential for Interaction with MAOIs—Adverse reactions, some serious, have been reported in patients who recently discontinued an MAOI and started on venlafaxine, or who recently discontinued venlafaxine prior to initiation of an MAOI. These reactions included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. Effexor XR should not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. At least 7 days should be allowed after stopping venlafaxine before starting an MAOI. Serotonin Syndrome**—The development of potentially life-threatening serotonin syndrome may occur with Effexor XR treatment, particularly with (i) concomitant use of serotonergic drugs and (ii) with drugs that impair metabolism of serotonin (see **CONTRAINDICATIONS—MAOIs**). If concomitant treatment of Effexor XR with an SSRI, SNRI, or a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with serotonin precursors (such as tryptophan supplements) is not recommended. **Sustained Hypertension**—Venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular monitoring of BP is recommended. For patients experiencing sustained increase in BP, consider either dose reduction or discontinuation. **Mydriasis**—Mydriasis has been reported; monitor patients with raised intraocular pressure or at risk of acute narrow-angle glaucoma (angle-closure glaucoma). **PRECAUTIONS: General—*Discontinuation of Treatment with Effexor XR*** Abrupt discontinuation or dose reduction of venlafaxine at various doses is associated with new symptoms, the frequency of which increased with increased dose level and longer duration of treatment. Symptoms include agitation, anorexia, anxiety, confusion, coordination impaired, diarrhea, dizziness, dry mouth, dysphoric mood, emotional lability, fasciculation, fatigue, headaches, hypomania, insomnia, irritability, lethargy, nausea, nervousness, nightmares, seizures, sensory disturbances (e.g., paresthesias such as electric shock sensations), somnolence, sweating, tinnitus, tremor, vertigo, and vomiting. Monitor patients when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, continue decreasing the dose at a more gradual rate. ***Insomnia and Nervousness:*** Treatment-emergent insomnia and nervousness have been reported. In Phase 3 trials, insomnia led to drug discontinuation in 1% of both depressed patients and Panic Disorder (PD) patients and in 3% of both Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD) patients. Nervousness led to drug discontinuation in 0.9% of depressed patients, in 2% of GAD patients, and in 0% of SAD and PD patients. ***Changes in Weight: Adult Patients:*** in short-term MDD trials, 7% of Effexor XR patients had ≥5% loss of body weight and 0.1% discontinued for weight loss. In 6-month GAD studies, 3% of Effexor XR patients had ≥7% loss of body weight, and 0.3% discontinued for weight loss in 8-week studies. In 12-week SAD trials, 3% of Effexor XR patients had ≥7% loss of body weight and no patients discontinued for weight loss. In 12-week PD trials, 3% of Effexor XR patients had ≥7% loss of body weight, and no patients discontinued for weight loss. The safety and efficacy of venlafaxine in combination with weight loss agents, including phentermine, have not been established. Coadministration of Effexor XR and weight loss agents is not recommended. Effexor XR is not indicated for weight loss alone or in combination with other products. ***Pediatric Patients:*** Weight loss was seen in patients aged 6-17 receiving Effexor XR. More Effexor XR patients than placebo patients experienced weight loss of at least 3.5% in both MDD and GAD studies (18% of Effexor XR patients vs. 3.6% of placebo patients; $P<0.001$) and the SAD study (47% of Effexor XR patients vs. 14% of placebo patients; $P<0.001$). Weight loss was not limited to patients with treatment-emergent anorexia (decreased appetite). Children and adolescents in a 6-month MDD study had increases in weight less than expected based on data from age- and sex-matched peers. The difference between observed and expected weight gain was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Height: Pediatric Patients:*** In 8-week GAD studies, Effexor XR patients aged 6-17 grew an average of 0.3 cm (n=122), while placebo patients grew an average of 1.0 cm (n=132); $P=0.041$. This difference in height increase

was most notable in patients <12. In 8-week MDD studies, Effexor XR patients grew an average of 0.8 cm (n=146), while placebo patients grew an average of 0.7 cm (n=147). During the 16-week, placebo-controlled SAD study, both the Effexor XR (n=109) and the placebo (n=112) patients grew an average of 1.0 cm. In the 6-month MDD study, children and adolescents had height increases less than expected based on data from age- and sex-matched peers. The difference between observed and expected growth rates was larger for children <12 years old than for adolescents ≥12 years old. ***Changes in Appetite***: ***Adult Patients***: Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. ***Pediatric Patients***: Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. In the placebo-controlled trial for SAD, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Effexor XR and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Effexor XR and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo. ***Activation of Mania/Hypomania***: Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. ***Hyponatremia***: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. ***Seizures***: In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. ***Abnormal Bleeding***: Abnormal bleeding (most commonly ecchymosis) has been reported. ***Serum Cholesterol Elevation***: Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. ***Interstitial Lung Disease and Eosinophilic Pneumonia***: These have been rarely reported. Consider the possibility of these events in venlafaxine patients who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation and should consider discontinuation of venlafaxine. ***Use in Patients With Concomitant Illness***: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient Medication Guide called *"Antidepressant Medicines, Depression and Other Serious Mental Illnesses, and Suicidal Thoughts or Actions"* is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk**: Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients 1) about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities; 2) to avoid alcohol while taking Effexor XR; and 3) about the risk of serotonin syndrome with the concomitant use of Effexor XR and triptans, tramadol, tryptophan supplements, or other serotonergic agents. Patients should be advised to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations and nutritional supplements they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena; or 4) if they have a history of glaucoma or increased intraocular pressure. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions**—***Alcohol***: A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine***: Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam***: A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol***: Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. ***Lithium***: A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. ***Drugs Highly Bound to Plasma Proteins***: Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. ***Drugs That Inhibit Cytochrome P450 Isoenzymes***: CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. ***Drugs Metabolized by Cytochrome P450 Isoenzymes***: Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. ***Imipramine***: Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. ***Risperidone***: Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4**: Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. ***Indinavir***: In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2**: Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9**: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19**: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). ***MAOIs***: See **CONTRAINDICATIONS** and **WARNINGS**. ***CNS-Active Drugs***: Use caution with concomitant use of venlafaxine and other CNS-active drugs. **Serotonergic Drugs and Triptans (see WARNINGS: Serotonin Syndrome)**: Based on the mechanism of action of Effexor XR and the potential for serotonin syndrome, caution is advised when Effexor XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's wort. If concomitant treatment of Effexor XR with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with tryptophan supplements is not recommended. ***Electroconvulsive Therapy (ECT)***: There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—***Carcinogenesis***: There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. ***Mutagenesis***: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. ***Impairment of Fertility***: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m^2 basis. **Pregnancy**—***Teratogenic Effects***—***Pregnancy Category C***: Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m^2 basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. ***Nonteratogenic Effects***: Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS**: ***Associated with Discontinuation of Treatment***—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD***—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. ***Vital Sign Changes***: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). ***Laboratory Changes***: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. ***Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR***—N=6,670. "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease, involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage as opposed to some characteristic(s) of venlafaxine-treated patients is not clear. Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. In managing overdosage, consider the possibility of multiple drug involvement. Consider contacting a poison control center for additional information on the treatment of overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). **DOSAGE AND ADMINISTRATION**: Consult full prescribing information for dosing instructions. **Switching Patients to or From an MAOI**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. At least 7 days should be allowed after stopping Effexor XR before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**). This brief summary is based on Effexor XR Prescribing Information W10404C027, revised May 2007.

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The Department of Psychiatry at The University at Buffalo is seeking an academic psychiatrist at the Assistant, Associate or Professor level with the interest and potential to develop a sustained, independent research program. This is a tenure track position with 50% fully protected time for the successful applicant to develop their research program. Resources for this recruitment include financial support for 1 to 2 additional faculty to work closely with the successful candidate and for part-time secretarial support. We are particularly interested in clinical scientists with established research programs in cognitive/behavioral neuroscience, clinical trials research, clinical psychopharmacology, psychoneuroimmunology, clinical/genetic epidemiology, or PTSD/mood disorders. Salary and benefits are excellent and commensurate with qualifications.

QUALIFICATIONS:

Successful candidates must have strong research credentials, including current or recent NIH funding as a principal investigator, and a willingness to mentor residents and faculty in research. Investigators whose research programs are closely associated with their clinical work are of particular interest.

The Department of Psychiatry and the School of Medicine have outstanding resources. The Department has an excellent reputation in the medical school and has a prominent teaching program for medical students. The residency programs in general psychiatry and child/adolescent psychiatry are thriving and there is a new geriatrics fellowship. The University and Chair are committed to expanding the research capacities of the Department. The School of Medicine and Biomedical Sciences has organized a consortium of affiliated hospitals offering a wide range of clinical settings and Department of Psychiatry faculty treat patients in many of these settings. This represents a rich and diverse source of potential participants for research programs. In addition, the department maintains relationships with a number of other research and health centers that provide opportunities for collaborative research, including the Buffalo Center of Excellence in Bioinformatics, the Roswell Park Cancer Institute, the UB-VA Center for Positron Emission Tomography, the Research Institute on Addictions, and The VA Western New York Healthcare System with a primary site in Buffalo.

Women and minorities are encouraged to apply. The University at Buffalo is an Equal Opportunity/Affirmative Action employer. Send cover letter describing clinical and research interests, resume, sample publications, and three letters of recommendation to:

Margaret Ubler-Otoka
Assistant to the Chair
Department of Psychiatry
School of Medicine and Biomedical Sciences
University at Buffalo
ECMC Room 1166
462 Grider Street
Buffalo, NY 14215

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brenda.chambers@ministryhealth.org

VA Medical Center

PSYCHIATRIST

The Lebanon VA Medical Center is recruiting for Psychiatrists (3 FT & 1 PT) to provide outpatient, inpatient and substance abuse psychiatric services. Positions available at Lebanon and York facilities. Sign-on bonus authorized. Must be U.S. citizen or permanent resident and possess full, current and unrestricted state license to practice medicine.

Please respond with CV to:
VA Medical Center
James Sumlin (121)
1700 S. Lincoln Avenue
Lebanon, PA 17042
Phone: (717) 228-5971
email: james.sumlin@va.gov
EOE

MEDICAL DIRECTOR
Child & Adolescent Services

South Oaks Hospital, Long Island, NY is a comprehensive mental health facility conveniently located on the Nassau/Suffolk County Border. We seek to create a work environment that fosters professional growth and development through communication and learning.

Our Behavioral Services for Children, Adolescents and Adults offers treatment programs in both inpatient and outpatient settings. The Medical Director will provide treatment, consultation and will work closely with service directors. Some work with adults and patients with chemical dependency is required. Qualified candidate must be a Board Certified Child/Adolescent Psychiatrist.

We offer an excellent compensation package of $200,000+ and noncontributory medical benefits and matching 401K with enhancements. All professional expenses including professional liability insurance are provided by the hospital.

Forward CV to: Medical Director
South Oaks Hospital
400 Sunrise Highway
Amityville, NY 11701
Email: yupadhyay@south-oaks.org

CLINICAL DIRECTOR (PSYCHIATRIC)
Physician Program Manager III

Maryland Department of Health and Mental Hygiene, Clifton T. Perkins Hospital Center, Jessup, MD, is seeking a professional medical and psychiatric worker as a senior management and supervisory level. This position is responsible for the overall quality of clinical services at the hospital center. This hospital is Maryland's only maximum security psychiatric hospital and community forensic program, and is JCAHO accredited. This position coordinates this hospital's services with those of Community Forensic Services, and provides liaison with other state hospitals. The incumbent will: develop and implement programs, policies procedures to provide assessment and treatment of patient needs within the areas of pretrial evaluation and inpatient care to include medical clinical operations; provide direct supervision to all physician staff (psychiatrists, generalists, and consultants), and to the department directors of pharmacy, nursing, psychology, social work, creative and prevocational therapies, and specialized services; Chair Formal Medical Staff meetings, ensure coverage of pretrial and inpatient care units, lead Clinical Review Panels, provide COMAR and JCAHO Clinical Director required oversight functions (e.g. seclusion and restraint); provide oversight for all Medical Staff Monitoring Functions and Therapeutics, Medical Records, Ethics, Credentialing and Privileging, Infection Control) and monitor Medical Staff CQI requirements; and serve on CTPHC Facility Internal Governing Body, Quality Council, Clinical/Forensic Review Board, Root Cause Analysis Team; and provide Inpatient Treatment Team and Office of Pretrial Evaluation Services oversight, supervision and consultation.

Requirements: MD degree, Board Certification in Psychiatry, and two years of medical practice as a Psychiatrist, preferably at a supervisory or administrative level. Five years of medical practice in psychiatry may be substituted for the Board Certification.
Desirable Qualifications: Board Certification in Psychiatry, and specialty training and/or experience in forensic psychiatry. Current license to practice medicine in Maryland required prior to appointment.
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Mail application to:

Mr. Mark Townend, Chief of Recruitment
Department of Health and Mental Hygiene
201 West Preston Street, Room 114-B
Baltimore, MD 21201

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PSYCHIATRISTS

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

Applicants are required to have expertise in treatment of at least one of the following patient populations: the seriously mentally ill, PTSD or provision of mental health in primary care clinics.

In addition to its close proximity to the metropolitan Austin area famous for its live entertainment, Central Texas offers affordable housing, excellent schools, one of the lowest costs of living in the country and year-round recreational opportunities highlighted by the lakes and rivers of the Texas Hill Country. Texas has no state income tax.

Candidates must be US citizens or permanent residents, as well as possess a valid and unrestricted medical license in at least one state. Reasonable accommodation provided to any applicant with disabilities. Applicants are subject to drug testing.

EOE

Please Fax or send CV to:
Mary P. Doerfler, Physician Recruiter
Central Texas Veterans Health Care System
1901 Veterans Memorial Drive, Temple, TX 76504
FAX (254) 743-1412 , Voice (254) 743-0049
Mary.Doerfler@va.gov

VA Northern California
Clinical Psychologist (LRC)

The VA Northern California Health Care System, affiliated with the UC Davis School of Medicine, is seeking a Clinical Psychologist to function as the Local Recovery Coordinator to join the Sacramento VA Medical Center at Mather. Ideally, candidates should be suitable for joint appointment to the U.C. Davis faculty, with rank and series dependent on credentials and experience. This licensed psychologist functions as a champion and advocate for the recovery model and also serves as a recovery ombudsman to the Associate Chief of Staff for Mental Health, program managers, and staff on recovery and implementation of recovery oriented services across 9 locations in Northern California.

The VA offers a highly competitive salary and a comprehensive benefits package. Applicants selected for this position will be eligible to apply for an award up to the maximum limitation under the provisions of the Education Debt Reduction Program. Candidates must have graduated from an APA-accredited graduate program and APA-accredited internship program and must be a U.S. Citizen or PRA.

The VA is an Equal Opportunity Employer.

Please send inquiry and CV to:

Sacramento VAMC (NCHS)
Human Resources (05/SMAT)
Attn: Tamiko Greely, Clinical Psychologist (LRC) Search
10535 Hospital Way
Mather, CA 95655
Fax (916) 364-0239

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Monmouth Medical Center has the following opportunity available:

CHAIR, DEPARTMENT OF PSYCHIATRY

Monmouth Medical Center, located in Long Branch, NJ, an affiliate of the St. Barnabas Health Care System, is seeking a Chair of Psychiatry to lead the clinical and educational activities of the Department, and to establish research opportunities through the Saint Barnabas Health Care System Research Institute. This is an outstanding opportunity for a visionary leader to foster inpatient and outpatient psychiatric services at Monmouth, and develop innovative programs throughout the Saint Barnabas Health Care System. The Chair is also responsible for all teaching activities within the Department, including medical student education through our long-standing affiliation with Drexel University College of Medicine.

MD degree or equivalent and Board certification in psychiatry is necessary, with academic credentials for a faculty appointment at Drexel University College of Medicine. Must show a record of achievement in patient care, administration and education, and have an interest in fostering research.

We offer the finest career advantages and life-friendly opportunities – please forward a letter of interest and current curriculum vitae to: **Allan R. Tunkel, MD, PhD, Chair of the Psychiatry Search Committee at: atunkel@sbhcs.com.**

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PSYCHIATRISTS

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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.

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 consultation-liaison psychiatry.
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- 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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For more information, call Dru Meredith, Physician Recruiter at 419-557-7885, or e-mail resume to meredid@firelands.com, fax 419-557-7235.

PSYCHIATRIST

Smoky Mountain Center seeks a highly qualified Child and or Adult Psychiatrist who can provide thorough psychiatric evaluation and diagnosis, initiates and monitors psychopharmacologic treatments and provides consultations to staff and other medical doctors as needed. Will evaluate and interpret related reports developed by physicians, psychologist, nurses, social workers and other professional personnel. Salary will be determined by candidate's qualifications and position will be open until filled. Smoky Mountain Center is a Local Government agency with excellent comprehensive benefits that include: Local Government Retirement, 5% agency match 401k, annual, sick and holiday leave, affordable comprehensive health and dental insurance.

Smoky Mountain Center is located in a most prestigious and beautiful area of Western North Carolina. The area offers tranquility, beautiful scenery and a variety of cultural activities.

Additional info about the agency and this employment opportunity can be found at: www.smokymountaincenter.com/employment.asp

Interested applicants should submit a state application to:

Smoky Mountain Center
Attn: Monica Jenkins
PO Box 127
Sylva, NC 28779
Email: jenkimon@smokymountaincenter.com
Phone: (828) 586-5501 ext 1100
Fax: (828) 586-3965

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MAYO CLINIC

C-L/Psychosomatic Medicine Psychiatrist

Scottsdale, Arizona

Mayo Clinic is known locally, nationally and internationally for outstanding achievements in patient care, research, and education. In Arizona, Mayo Clinic is a 360-physician integrated practice, focusing on high-quality, compassionate medical care delivered in a multi-specialty academic environment. Education and research are an integral part of the Mayo Clinic Model of Care.

The Division of Psychiatry at Mayo Clinic in Arizona is seeking a consultation-liaison (psychosomatic medicine) psychiatrist. Our staff includes four psychiatrists, four psychologists, plus several other allied health staff. Our practice is focused on the care of medically ill patients. Our clinical priorities are patients with cancer, neurologic disease, cardiovascular disease, and transplantation issues. Psychiatrists rotate between the inpatient consultation service (averaging 45 consultations a month) and a busy outpatient consultation practice. Continuing care is a relatively minor part of the practice and is generally limited to patients with active medical illness allowing their psychiatric care to be integrated with their other care providers. All psychiatrists have call responsibilities which include coverage one week at a time approximately every five weeks.

The desired individual will have a scholarly perspective and enjoy education and/or research activities. The position includes an academic appointment with the Mayo Clinic College of Medicine. Proficiency in Spanish would be an asset to our institution.

Mayo Clinic offers competitive compensation and comprehensive benefits. To learn more about Mayo Clinic and Arizona, and to apply online, please visit **www.mayoclinic.org**

For consideration, please forward current curriculum vitae to:

Lois E. Krahn, M.D.
Mayo Clinic
13400 E. Shea Boulevard
Scottsdale, AZ 85259
Email: Krahn.Lois@mayo.edu
(480) 301-8297

Mayo Clinic is an affirmative action and equal opportunity educator and employer. Post offer/pre-employment drug screening is required.

Academic Community Psychiatrist

Washington Hospital Center Department of Psychiatry is a leader in providing full continuum of inpatient, outpatient, psychosomatic medicine and substance abuse treatment in the Washington DC Metropolitan area. The Outpatient Services of the Department of Psychiatry at Washington Hospital Center seeks academic psychiatrist.

The psychiatrist will provide outpatient community psychiatric care at Trinity Square Behavioral Health Services, the outpatient section of the Department of Psychiatry, and have teaching responsibilities in community psychiatry.

Candidates must be board certified in general psychiatry and eligible for a District of Columbia medical license. Qualified candidates should send a letter of interest and curriculum vitae to:

Karen M. Johnson, MD
Associate Chair & Director, Psychosomatic Services
Department of Psychiatry
Washington Hospital Center
110 Irving St., NW EB-3105
Washington D.C. 20010
Fax # (202) 877-7552
Email – Inga.L.Ricks@medstar.net

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DIRECTOR - CENTER FOR ALZHEIMER DISEASE AND RELATED DISORDERS (CADRD)

Southern Illinois University School Of Medicine (SIUSM) is seeking an accomplished clinician scientist to become Director of our Center for Alzheimer Disease and Related Disorders (CADRD), consistent with the mission of SIUSM to become a leading research institution. This tenured/tenure track position will also hold an endowed professorship in Alzheimer disease research.

The CADRD is funded by a large annual grant from the State of Illinois and has a history of continued funding for more than 17 years. The Center has an outreach network of 26 hospitals or clinics throughout Illinois, a brain bank, a neuropsychology program, and specialty clinics for the treatment of Alzheimer disease and other degenerative dementias. Currently, five faculty members are actively engaged in Alzheimer research, with one additional open position. In addition, opportunities are available for collaborations with the Geriatric Center of Excellence, the Department of Psychiatry, and basic science departments such as Pharmacology.

The Director of the SIU CADRD reports to the Dean of SIUSM (institutional and administrative matters) and to the Chair of an appropriate Department (departmental and academic matters). The Director will lead the CADRD, holding responsibility for budget decisions, research direction, staffing, and interactions with other departments, institutes, and agencies. Responsibilities also include working with the Illinois legislature and Departments of Public Health, Aging, Education and Public Aid to develop strategies, external support, and collaborative efforts that will advance the aims of the CADRD in the areas of outreach, teaching, research, and clinical service.

Applicants must be board-certified in a specialty relevant to the activities of SIU CADRD and maintain an active externally-funded research program focused on dementia. Illinois licensure is required prior to employment. Deadline to apply is December 31, 2007 or until filled. Interested applicants should send their CV by mail or email to:

Carol Forestier
Secretary for Dr. Leonard Rybak, MD, Ph.D.
Chairman of Search Committee
SIU School of Medicine
P.O. Box 19643
Springfield, IL 62794-9643
cforestier@siumed.edu

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BRIEF SUMMARY. See package insert for full prescribing information.

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

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

CONTRAINDICATIONS — *QT Prolongation:* Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS—Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see Boxed Warning). *QT Prolongation and Risk of Sudden Death:*** **GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT_c prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec. *Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS — *General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis)**. Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine,* 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole,* a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. *Cimetidine,* 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives,* ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan,* a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS — *Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Schizophrenia: Body as a Whole — *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System — *Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System — *Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine — *Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders — *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System — *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System — *Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System — *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages — *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses — *Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System — *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE — *Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE** — In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/95).

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

In schizophrenia…

Rapid improvement with low EPS[1,2]

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

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

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

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

GEODON®
Oral Capsules *(ziprasidone HCl)*
and ***Injection*** *(ziprasidone mesylate)*

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

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

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

Please see brief summary of prescribing information on adjacent page.