Rozerem™
ramelteon 8-mg tablets

Takeda

Brief Summary of Prescribing Information
05-1114

ROZEREM™
(ramelteon) Tablets

INDICATIONS AND USAGE
ROZEREM is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

CONTRAINDICATIONS
ROZEREM is contraindicated in patients with a hypersensitivity to ramelteon or any components of the ROZEREM formulation.

WARNINGS
Since 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 a reasonable period 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 cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with ROZEREM during the clinical development program.

ROZEREM should not be used by patients with severe hepatic impairment.

ROZEREM should not be used in combination with fluvoxamine (see **PRECAUTIONS: Drug Interactions**).

A variety of cognitive and behavior changes have been reported to occur in association with the use of hypnotics. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotics.

Patients should avoid engaging in hazardous activities that require concentration (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

After taking ROZEREM, patients should confine their activities to those necessary to prepare for bed.

PRECAUTIONS
General
ROZEREM has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations.

Patients should be advised to exercise caution if they consume alcohol in combination with ROZEREM.

Use in Adolescents and Children
ROZEREM has been associated with an effect on reproductive hormones in adults, e.g. decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ROZEREM may have on the reproductive axis in developing humans (see **Pediatric Use**).

Information for Patients
Patients should be advised to take ROZEREM within 30 minutes prior to going to bed and should confine their activities to those necessary to prepare for bed.

Patients should be advised to avoid engaging in hazardous activities (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

Patients should be advised that they should not take ROZEREM with or immediately after a high fat meal.

Patients should be advised to consult their health care provider if they experience worsening of insomnia or any new behavioral signs or symptoms of concern.

Patients should consult their health care provider if they experience one of the following: cessation of menses or galactorrhea in females, decreased libido, or problems with fertility.

Laboratory Tests
No standard monitoring is required.

For patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels and testosterone levels should be considered as appropriate.

Drug Interactions
ROZEREM has a highly variable inter-subject pharmacokinetic profile (approximately 100% coefficient of variation in C_{max} and AUC). As noted above, CYP1A2 is the major isozyme involved in the metabolism of ROZEREM; the CYP2C subfamily and CYP3A4 isozymes are also involved to a minor degree.

Effects of Other Drugs on ROZEREM Metabolism
Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ROZEREM 16 mg and fluvoxamine, the $AUC_{0\text{-}inf}$ for ramelteon increased approximately 190-fold, and the C_{max} increased approximately 70-fold, compared to ROZEREM administered alone. ROZEREM should not be used in combination with fluvoxamine (See WARNINGS). Other less potent CYP1A2 inhibitors have not been adequately studied. ROZEREM should be administered with caution to patients taking less strong CYP1A2 inhibitors.

Rifampin (strong CYP enzyme inducer): Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease of approximately 80% (40% to 90%) in total exposure to ramelteon and metabolite M-II, (both $AUC_{0\text{-}inf}$ and C_{max}) after a single 32 mg dose of ROZEREM. Efficacy may be reduced when ROZEREM is used in combination with strong CYP enzyme inducers such as rifampin.

Ketoconazole (strong CYP3A4 inhibitor): The $AUC_{0\text{-}inf}$ and C_{max} of ramelteon increased by approximately 84% and 36%, respectively, when a single 16 mg dose of ROZEREM was administered on the fourth day of ketoconazole 200 mg twice daily administration, compared to administration of ROZEREM alone. Similar increases were seen in M-II pharmacokinetic variables. ROZEREM should be administered with caution in subjects taking strong CYP3A4 inhibitors such as ketoconazole.

Fluconazole (strong CYP2C9 inhibitor): The total and peak systemic exposure ($AUC_{0\text{-}inf}$ and C_{max}) of ramelteon after a single 16 mg dose of ROZEREM was increased by approximately 150% when administered with fluconazole. Similar increases were also seen in M-II exposure. ROZEREM should be administered with caution in subjects taking strong CYP2C9 inhibitors such as fluconazole.

Interaction studies of concomitant administration of ROZEREM with fluoxetine (CYP2D6 inhibitor), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon or the M-II metabolite.

Effects of ROZEREM on Metabolism of Other Drugs
Concomitant administration of ROZEREM with omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), and warfarin (CYP2C9 [S]/CYP1A2 [R] substrate) did not produce clinically meaningful changes in peak and total exposures to these drugs.

Effect of Alcohol on Rozerem
Alcohol: With single-dose, daytime co-administration of ROZEREM 32 mg and alcohol (0.6 g/kg), there were no clinically meaningful or statistically significant effects on peak or total exposure to ROZEREM. However, an additive effect was seen on some measures of psychomotor performance (i.e., the Digit Symbol Substitution Test, the Psychomotor Vigilance Task Test, and a Visual Analog Scale of sedation) at some post-dose time points. No additive effect was seen on the Delayed Word Recognition Test. Because alcohol by itself impairs performance, and the intended effect of ROZEREM is to promote sleep, patients should be cautioned not to consume alcohol when using ROZEREM.

Drug/Laboratory Test Interactions
ROZEREM is not known to interfere with commonly used clinical laboratory tests. In addition, *in vitro* data indicate that ramelteon does not cause false-positive results for benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screening methods *in vitro*.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Carcinogenesis
In a two-year carcinogenicity study, $B6C3F_1$ mice were administered ramelteon at doses of 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage. Male mice exhibited a dose-related increase in the incidence of hepatic tumors at dose levels ≥100 mg/kg/day including hepatic adenoma, hepatic carcinoma, and hepatoblastoma. Female mice developed a dose-related increase in the incidence of hepatic adenomas at dose levels ≥ 300 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors in male mice was 30 mg/kg/day (103-times and 3-times the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the maximum recommended human dose [MRHD] based on an area-under-the-curve [AUC] comparison). The no-effect level for hepatic tumors in female mice was 100 mg/kg/day (827-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male and female rats were administered ramelteon at doses of 0, 15, 60, 250 or 1000 mg/kg/day by oral gavage. Male rats exhibited a dose-related increase in the incidence of hepatic adenoma and benign Leydig cell tumors of the testis at dose levels ≥ 250 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. Female rats exhibited a dose-related increase in the incidence of hepatic adenoma at dose levels ≥ 60 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors and benign Leydig cell tumors in male rats was 60 mg/kg/day (1,429-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC). The no-effect level for hepatic tumors in female rats was 15 mg/kg/day (472-times and 16-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The development of hepatic tumors in rodents following chronic treatment with non-genotoxic compounds may be secondary to microsomal enzyme induction, a mechanism for tumor generation not thought to occur in humans. Leydig cell tumor development following treatment with non-genotoxic compounds in rodents has been linked to reductions in circulating testosterone levels with compensatory increases in luteinizing hormone release, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of luteinizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily ramelteon administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma testosterone levels. In the same study, luteinizing hormone levels were elevated over a 24 hour period after the last ramelteon treatment; however, the durability of this luteinizing hormone finding and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following ramelteon treatment occurred at plasma levels of ramelteon and M-II in excess of mean clinical plasma concentrations at the MRHD, the relevance of both rodent hepatic tumors and benign rat Leydig cell tumors to humans is not known.

Mutagenesis
Ramelteon was not genotoxic in the following: *in vitro* bacterial reverse mutation (Ames) assay; *in vitro* mammalian cell gene mutation assay using the mouse lymphoma $TK^{+/-}$ cell line; *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes; and in *in vivo* micronucleus assays conducted in mouse and rat. Ramelteon was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of S9 metabolic activation.

Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver S9 fraction used in the *in vitro* genetic toxicology studies described above, exceeded the concentration of ramelteon; therefore, the genotoxic potential of the M-II metabolite was also assessed in these studies.

Impairment of Fertility
Ramelteon was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 6, 60, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a ramelteon dose up to 600 mg/kg/day (786-times higher than the MRHD on a mg/m^2 basis). Irregular estrus cycles, reduction in the number of implants, and reduction in the number of live embryos were noted with dosing females at ≥ 60 mg/kg/day (79-times higher than the MRHD on a mg/m^2 basis). A reduction in the number of corpora lutea occurred at the 600 mg/kg/day dose level. Administration of ramelteon up to 600 mg/kg/day to male rats for 7 weeks had no effect on sperm quality and when the treated male rats were mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of ramelteon at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with doses ≥ 60 mg/kg/day, but no effects were seen on implantation or embryo viability. The no-effect dose for fertility endpoints was 20 mg/kg/day in females (26-times the MRHD on a mg/m^2 basis) and 600 mg/kg/day in males (786-times higher than the MRHD on a mg/m^2 basis) when considering all studies.

Pregnancy: Pregnancy Category C
Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 times higher than the maximum recommended human dose [MRHD] on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women. Ramelteon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of ramelteon on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered ramelteon by oral gavage at doses of 0, 10, 40, 150, or 600 mg/kg/day during gestation days 6-17, which is the period of organogenesis in this species. Evidence of maternal toxicity and fetal teratogenicity was observed at doses greater than or equal to 150 mg/kg/day. Maternal toxicity was chiefly characterized by decreased body weight and, at 600 mg/kg/day, ataxia and decreased spontaneous movement. At maternally toxic doses (150 mg/kg/day or greater), the fetuses demonstrated visceral malformations consisting of diaphragmatic hernia and minor anatomical variations of the skeleton (irregularly shaped scapula). At 600 mg/kg/day, reductions in fetal body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 40 mg/kg/day (1,892-times and 45-times higher than the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the MRHD based on an area-under-the-curve [AUC] comparison). Pregnant rabbits were administered ramelteon by oral gavage at doses of 0, 12, 60, or 300 mg/kg/day during gestation days 6-18, which is the period of organogenesis in this species. Although maternal toxicity was apparent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was associated with any dose level. The no-effect level for teratogenicity was, therefore, 300 mg/kg/day (11,862-times and 99-times higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The effects of ramelteon on pre- and post-natal development in the rat were studied by administration of ramelteon to the pregnant rat by oral gavage at doses of 0, 30, 100, or 300 mg/kg/day from day 6 of gestation through parturition to postnatal (lactation) day 21, at which time offspring were weaned. Maternal toxicity was noted at doses of 100 mg/kg/day or greater and consisted of reduced body weight gain and increased adrenal gland weight. Reduced body weight during the post-weaning period was also noticed in the offspring of the groups given 100 mg/kg/day and higher. Offspring in the 300 mg/kg/day group demonstrated physical and developmental delays including delayed eruption of the lower incisors, a delayed acquisition of the righting reflex, and an alteration of emotional response. These delays are often observed in the presence of reduced offspring body weight but may still be indicative of developmental delay. An apparent decrease in the viability of offspring in the 300 mg/kg/day group was likely due to altered maternal behavior and function observed at this dose level. Offspring of the 300 mg/kg/day group also showed evidence of diaphragmatic hernia, a finding observed in the embryo-fetal development study previously described. There were no effects on the reproductive capacity of offspring and the resulting progeny were not different from those of vehicle-treated offspring. The no-effect level for pre- and postnatal development in this study was 30 mg/kg/day (39-times higher than the MRHD on a mg/m^2 basis).

Labor and Delivery
The potential effects of ROZEREM on the duration of labor and/or delivery, for either the mother or the fetus, have not been studied. ROZEREM has no established use in labor and delivery.

Nursing Mothers
Ramelteon is secreted into the milk of lactating rats. It is not known whether this drug is excreted in human milk. No clinical studies in nursing mothers have been performed. The use of ROZEREM in nursing mothers is not recommended.

Pediatric Use
Safety and effectiveness of ROZEREM in pediatric patients have not been established. Further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent patients.

Geriatric Use
A total of 654 subjects in double-blind, placebo-controlled, efficacy trials who received ROZEREM were at least 65 years of age; of these, 199 were 75 years of age or older. No overall differences in safety or efficacy were observed between elderly and younger adult subjects.

ADVERSE REACTIONS
Overview
The data described in this section reflect exposure to ROZEREM in 4251 subjects, including 346 exposed for 6 months or longer, and 473 subjects for one year.

Adverse Reactions Resulting in Discontinuation of Treatment
Five percent of the 3594 individual subjects exposed to ROZEREM in clinical studies discontinued treatment owing to an adverse event, compared with 2% of the 1370 subjects receiving placebo. The most frequent adverse events leading to discontinuation in subjects receiving ROZEREM were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%).

ROZEREM Most Commonly Observed Adverse Events in Phase 1-3 trials
The incidence of adverse events during the Phase 1 through 3 trials (% placebo, n=1370; % ramelteon [8 mg], n=1250) were: headache NOS (7%, 7%), somnolence (3%, 5%), fatigue (2%, 4%), dizziness (3%, 5%), nausea (2%, 3%), insomnia exacerbated (2%, 3%), upper respiratory tract infection NOS (2%, 3%), diarrhea NOS (2%, 2%), myalgia (1%, 2%), depression (1%, 2%), dysgeusia (1%, 2%), arthralgia (1%, 2%), influenza (0, 1%), blood cortisol decreased (0, 1%)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

DRUG ABUSE AND DEPENDENCE
ROZEREM is not a controlled substance.

Human Data: See the CLINICAL TRIALS section, Studies Pertinent to Safety Concerns for Sleep-Promoting Agents in the Complete Prescribing Information.

Animal Data. Ramelteon did not produce any signals from animal behavioral studies indicating that the drug produces rewarding effects. Monkeys did not self-administer ramelteon and the drug did not induce a conditioned place preference in rats. There was no generalization between ramelteon and midazolam. Ramelteon did not affect rotorod performance, an indicator of disruption of motor function, and it did not potentiate the ability of diazepam to interfere with rotorod performance.

Discontinuation of ramelteon in animals or in humans after chronic administration did not produce withdrawal signs. Ramelteon does not appear to produce physical dependence.

OVERDOSAGE
Signs and Symptoms
No cases of ROZEREM overdose have been reported during clinical development.

ROZEREM was administered in single doses up to 160 mg in an abuse liability trial. No safety or tolerability concerns were seen.

Recommended Treatment
General symptomatic and supportive measures should be used, along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate vital signs should be monitored, and general supportive measures employed.

Hemodialysis does not effectively reduce exposure to ROZEREM. Therefore, the use of dialysis in the treatment of overdosage is not appropriate.

Poison Control Center
As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may contact a poison control center for current information on the management of overdosage.

Rx only

Manufactured by:
Takeda Pharmaceutical Company Limited
540-8645 Osaka, JAPAN

Manufactured in:
Takeda Ireland Ltd.
Kilruddery, County Wicklow, Republic of Ireland

Marketed by:
Takeda Pharmaceuticals America, Inc.
475 Half Day Road
Lincolnshire, IL 60069

 PI02-0002-1

References: 1. Rozerem package insert, Takeda Pharmaceuticals America, Inc. **2.** Johnson MW, Suess PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative side effects. *Arch Gen Psychiatry.* In press.

FIRST IN A NOVEL CLASS OF SLEEP AGENTS

Start and stay with nonscheduled Rozerem—ZERO evidence of abuse or dependence

Clinical studies show no evidence of potential abuse, dependence, or withdrawal*

- **First and only**—nonscheduled prescription insomnia medication...not a controlled substance and approved for long-term use[1]
- **First and only**—prescription insomnia medication that targets the normal sleep-wake cycle[1]
- **First and only**—prescription insomnia medication with no evidence of abuse potential in clinical studies[1]
- **First and only**—prescription insomnia medication that does not promote sleep by CNS depression[1]
- **Promote sleep with Rozerem**—patients who took Rozerem fell asleep faster than those who took placebo[1]
- **One simple 8-mg dose**[1]

*Rozerem is not a controlled substance. A clinical abuse liability study showed no differences indicative of abuse potential between Rozerem and placebo at doses up to 20 times the recommended dose (N=14). Three 35-day insomnia studies showed no evidence of rebound insomnia or withdrawal symptoms with Rozerem compared to placebo (N=2082).[1,2]

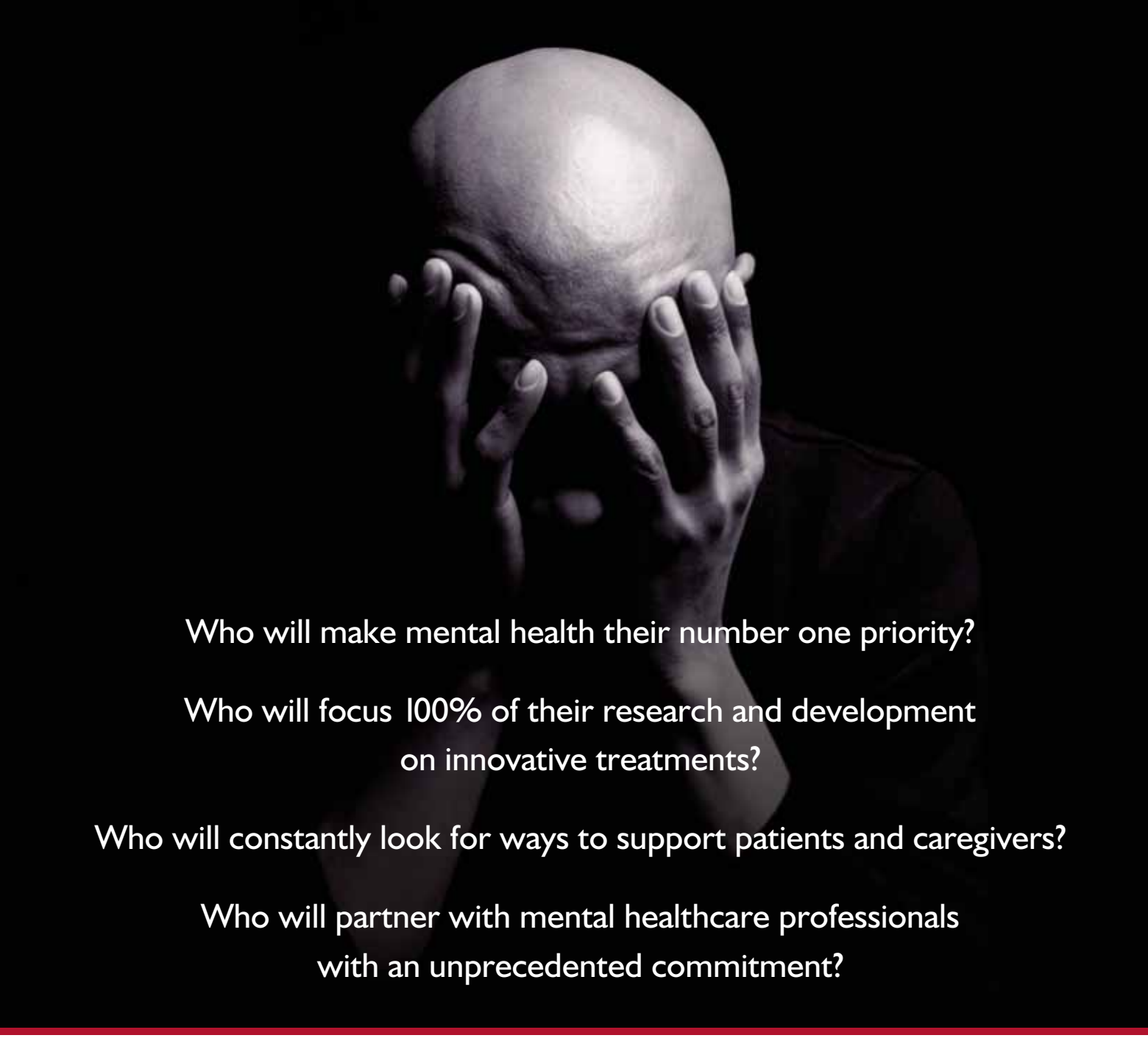
Please visit www.rozerem.com

Rozerem is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Rozerem can be prescribed for long-term use. Rozerem should not be used in patients with hypersensitivity to any components of the formulation, severe hepatic impairment, or in combination with fluvoxamine. Failure of insomnia to remit after a reasonable period of time should be medically evaluated, as this may be the result of an unrecognized underlying medical disorder. Hypnotics should be administered with caution to patients exhibiting signs and symptoms of depression. Rozerem has not been studied in patients with severe sleep apnea, severe COPD, or in children or adolescents. The effects in these populations are unknown. Avoid taking Rozerem with alcohol. Rozerem has been associated with decreased testosterone levels and increased prolactin levels. Health professionals should be mindful of any unexplained symptoms possibly associated with such changes in these hormone levels. Rozerem should not be taken with or immediately after a high-fat meal. Rozerem should be taken within 30 minutes before going to bed and activities confined to preparing for bed. The most common adverse events seen with Rozerem that had at least a 2% incidence difference from placebo were somnolence, dizziness, and fatigue.

Please see adjacent Brief Summary of Prescribing Information.

Rozerem™
ramelteon 8-mg tablets

Proven for sleep.
Nonscheduled for added safety.



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Who will constantly look for ways to support patients and caregivers?

Who will partner with mental healthcare professionals with an unprecedented commitment?

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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 treats the emotional, anxious, and painful somatic symptoms of depression.[1a,b,2*] Cymbalta also offers high rates of remission, so patients can feel more like themselves again.[1c†] To learn more about treating beyond the obvious, visit www.insidecymbalta.com

* 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**, and **Psychic Anxiety**. 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, $P \leq .001$.

References: 1. Data on file, Lilly Research Laboratories: a:CYM20060101A; b:CYM20060101B; c: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 and adolescents with major depressive disorder (MDD) and other psychiatric disorders.**
- **Patients started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.**
- **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 adult and pediatric patients being treated with an antidepressant for any indication should be 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 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.

Most common adverse events (≥5% and at least twice placebo) in MDD premarketing clinical trials were: nausea, dry mouth, constipation, fatigue, decreased appetite, somnolence, and increased sweating.

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 in Children and Adolescents—Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients. (*See* WARNINGS *and* PRECAUTIONS, Pediatric Use.)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

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

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 MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with MDD and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from some trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in any of these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, ie, beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face to face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for 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 pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder—A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (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 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 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 Monoamine Oxidase Inhibitors).

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, 1% (39/3732) of Cymbalta-treated patients had a >3 times the upper limit of normal elevation of ALT 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. Effect on Blood Pressure—In MDD clinical trials, Cymbalta treatment was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo. 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% (1/1139) of Cymbalta-treated patients and 0.1% (1/777) of placebo-treated patients. 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—Cymbalta has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with MDD, seizures occurred in 0.1% (1/1139) of Cymbalta-treated patients and 0% (0/777) of placebo treated patients. In placebo-controlled clinical trials in patients with diabetic peripheral neuropathy, seizures did not occur in any patients treated with either Cymbalta or placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder. 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 Cymbalta. Following abrupt discontinuation in MDD placebo-controlled clinical trials of up to 9 weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and at a significantly higher rate in Cymbalta-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

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. However, the electrocardiograms of 321 patients who received Cymbalta in MDD placebo-controlled clinical trials and had qualitatively normal ECGs at baseline were evaluated; Cymbalta was not associated with the development of clinically significant ECG abnormalities (*see* ADVERSE REACTIONS, Electrocardiogram Changes). In DPN placebo-controlled clinical trials, Cymbalta-treated patients did not develop abnormal ECGs at a rate different from that in placebo-treated patients (*see* ADVERSE REACTIONS, Electrocardiogram Changes). 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, small increases in fasting blood glucose were observed in Cymbalta-treated patients. HbA_{1c} was stable in both Cymbalta-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the Cymbalta and the routine care groups, but the mean increase was 0.3% greater in the Cymbalta-treated group. There was also a small increase in fasting blood glucose in the Cymbalta-treated group. Total cholesterol was increased in Cymbalta-treated patients (2 mg/dL) and decreased in the routine care group (6 mg/dL). 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 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

Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules PV 3608 AMP

triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (*see* WARNINGS, Serotonin Syndrome). The concomitant use of 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. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics.

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 clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN studies, 33% (357) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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. For both MDD and DPN 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).

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.

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 4 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 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***—Cymbalta treatment, for up to 9 weeks in MDD placebo-controlled clinical trials of 40 to 120 mg daily doses caused increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic compared to placebo and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg (*see* PRECAUTIONS). Cymbalta treatment, for up to 9 weeks in MDD placebo-controlled clinical trials and for up to 13 weeks in DPN placebo-controlled trials caused a small increase in heart rate compared to placebo of about 2 beats per minute. ***Weight Changes***—In MDD placebo-controlled clinical trials, patients treated with Cymbalta for up to 9 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 321 Cymbalta-treated patients with MDD and 169 placebo-treated patients in clinical trials lasting up to 8 weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, and QRS intervals between Cymbalta-treated and placebo-treated patients. Electrocardiograms were obtained from 528 Cymbalta-treated patients with DPN and 205 placebo-treated patients in clinical trials lasting up to 13 weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTc measurements between Cymbalta-treated and placebo-treated patients.

Postmarketing Spontaneous Reports—Adverse events reported rarely since market introduction that were temporally related to Cymbalta therapy include: hallucinations, rash, and urinary retention. The following adverse events were reported very rarely: alanine aminotransferase increased, alkaline phosphatase increased, anaphylactic reaction, angioneurotic edema, aspartate aminotransferase increased, bilirubin increased, extrapyramidal disorder, glaucoma, hepatitis, hypersensitivity, hypertensive crisis, hyponatremia, jaundice, mania, orthostatic hypotension (especially at the initiation of treatment), seizures, serotonin syndrome, Stevens-Johnson Syndrome, supraventricular arrhythmia, syncope (especially at initiation of treatment), syndrome of inappropriate antidiuretic hormone secretion (SIADH), 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 premarketing clinical trials, cases of acute ingestions up to 1400 mg, alone or in combination with other drugs, were reported with none being fatal. Postmarketing experience includes reports of overdoses, alone or in combination with other drugs, with duloxetine doses of almost 2000 mg. Fatalities have been very rarely reported, primarily with mixed overdoses, but also with duloxetine alone at a dose of 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 September 1, 2006

PV 3608 AMP PRINTED IN USA

Eli Lilly and Company
Indianapolis, IN 46285, USA

www.Cymbalta.com

Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules PV 3608 AMP


Success isn't just measured in years,
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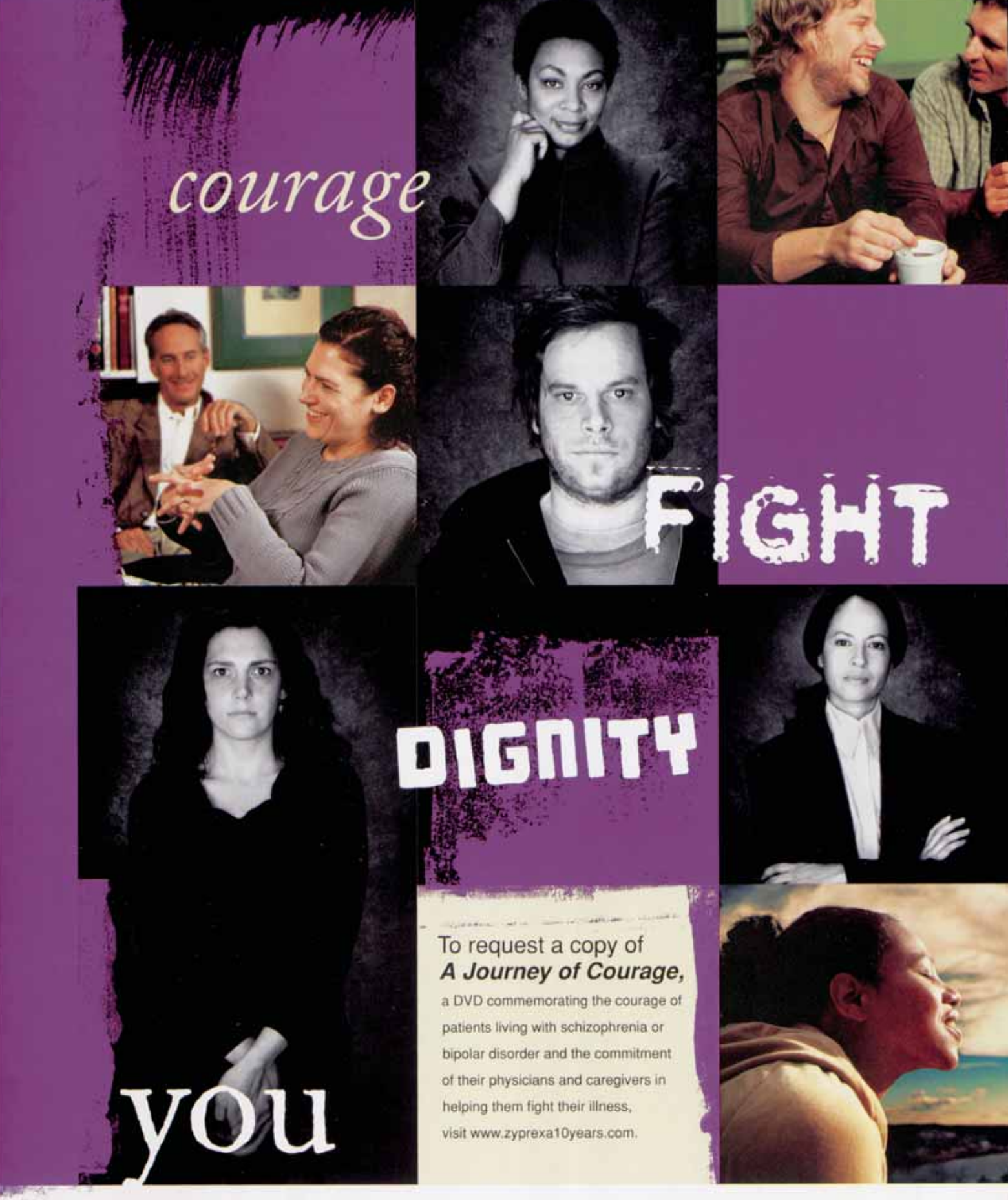

To request a copy of
A Journey of Courage,
a DVD commemorating the courage of patients living with schizophrenia or bipolar disorder and the commitment of their physicians and caregivers in helping them fight their illness, visit www.zyprexa10years.com.

ZYPREXA is approved for the treatment of schizophrenia, acute bipolar mania, and maintenance treatment in bipolar disorder.

See under flap on adjacent page for Important Safety Information, including boxed warning, and Brief Summary of Prescribing Information.

10 Years
And Moving Forward
1996 - 2006

We celebrate the moments of the last 10 years

that you've helped make possible.

Along with the 150,000 physicians[1] who last year prescribed ZYPREXA, Lilly is proud to be a part of the ongoing fight to make a difference in patients' lives.

The labeling for ZYPREXA includes a boxed warning:

- 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 elderly patients with dementia-related psychosis.

ZYPREXA®
Olanzapine

Important Safety Information for ZYPREXA® (olanzapine)

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 elderly patients with dementia-related psychosis.

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

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

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

Tardive dyskinesia (TD)—As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. If its signs and symptoms appear, discontinuation should be considered.

Orthostatic hypotension—In premarketing schizophrenia trials, some patients taking ZYPREXA may have experienced orthostatic hypotension associated with dizziness, tachycardia, and, in some cases, syncope (15/2500, 0.6%).

Seizures—Occurred infrequently in premarketing clinical trials (22/2500, 0.9%). ZYPREXA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

Effect on prolactin—Modest elevations of prolactin were seen with ZYPREXA in acute-phase schizophrenia trials (incidence 34% vs 13% with placebo), although mean changes from baseline to endpoint were not statistically significantly different between olanzapine and placebo. Some patients may have persisting modest prolactin elevations.

Transient, asymptomatic elevations of hepatic transaminase—In placebo-controlled schizophrenia trials, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of the normal range) were observed in 2% (6/243) of patients exposed to ZYPREXA compared to none (0/115) of the placebo patients. None of these patients developed jaundice. 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. Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

Special populations, elderly—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Olanzapine should be used with caution in patients at risk for aspiration pneumonia. In 5 studies in elderly patients with dementia-related psychosis, adverse events reported more commonly with olanzapine than with placebo were falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth, and visual hallucinations. Olanzapine should be used with caution in elderly patients with dementia. Olanzapine is not approved for treatment of patients with dementia-related psychosis.

Drug interactions—Coadministration of diazepam or ethanol with ZYPREXA may potentiate orthostatic hypotension. Lower doses of ZYPREXA should be considered in patients receiving concomitant therapy with fluvoxamine.

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

The most common treatment-emergent adverse events associated with ZYPREXA (vs placebo) in 6-week acute-phase schizophrenia trials were somnolence (26% vs 15%), dizziness (11% vs 4%), weight gain (6% vs 1%), personality disorder (COSTART term for nonaggressive objectionable behavior; 8% vs 4%), constipation (9% vs 3%), akathisia (5% vs 1%), and postural hypotension (5% vs 2%).

The most common treatment-emergent adverse events associated with ZYPREXA (vs placebo) in 3- and 4-week bipolar mania trials were somnolence (35% vs 13%), dry mouth (22% vs 7%), dizziness (18% vs 6%), asthenia (15% vs 6%), constipation (11% vs 5%), dyspepsia (11% vs 5%), increased appetite (6% vs 3%), and tremor (6% vs 3%).

1. IMS Health, National Prescription Audit Plus™, Jan-Dec 2005, ZYP20060810A.

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 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 a clinical trial involving 3 fixed oral dosage ranges compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

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, 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 rarely reported.

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

Literature revised March 20, 2006

PV 5195 AMP

Lilly **Eli Lilly and Company**
Indianapolis, IN 46285, USA

www.ZYPREXA.com

ZYPREXA® (Olanzapine Tablets)
ZYPREXA® ZYDIS® (Olanzapine Orally Disintegrating Tablets)
ZYPREXA® IntraMuscular (Olanzapine for Injection) PV 5195 AMP

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 (e.g., 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 C_{max} 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 C_{max} 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/m² basis). In this study there was a high incidence of early mortalities in males in the 30/20 mg/kg/d group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice and rats given olanzapine at 0.5 and 2 times the MHDOD respectively (mg/m² basis). In other studies, serum prolactin measurements of olanzapine showed elevations up to 4-fold in rats at the same doses used in the carcinogenicity studies. The relevance for human risk of the finding of prolactin mediated endocrine tumors in 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/m² basis). Diestrous was prolonged and estrous delayed at 0.6 times the MHDOD (mg/m² 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.

ZYPREXA® (Olanzapine Tablets)
ZYPREXA® ZYDIS® (Olanzapine Orally Disintegrating Tablets)
ZYPREXA® IntraMuscular (Olanzapine for Injection) PV 5195 AMP

KNOW THE FACTS

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

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

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Reference: 1. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res.* 2005;80:45-53.

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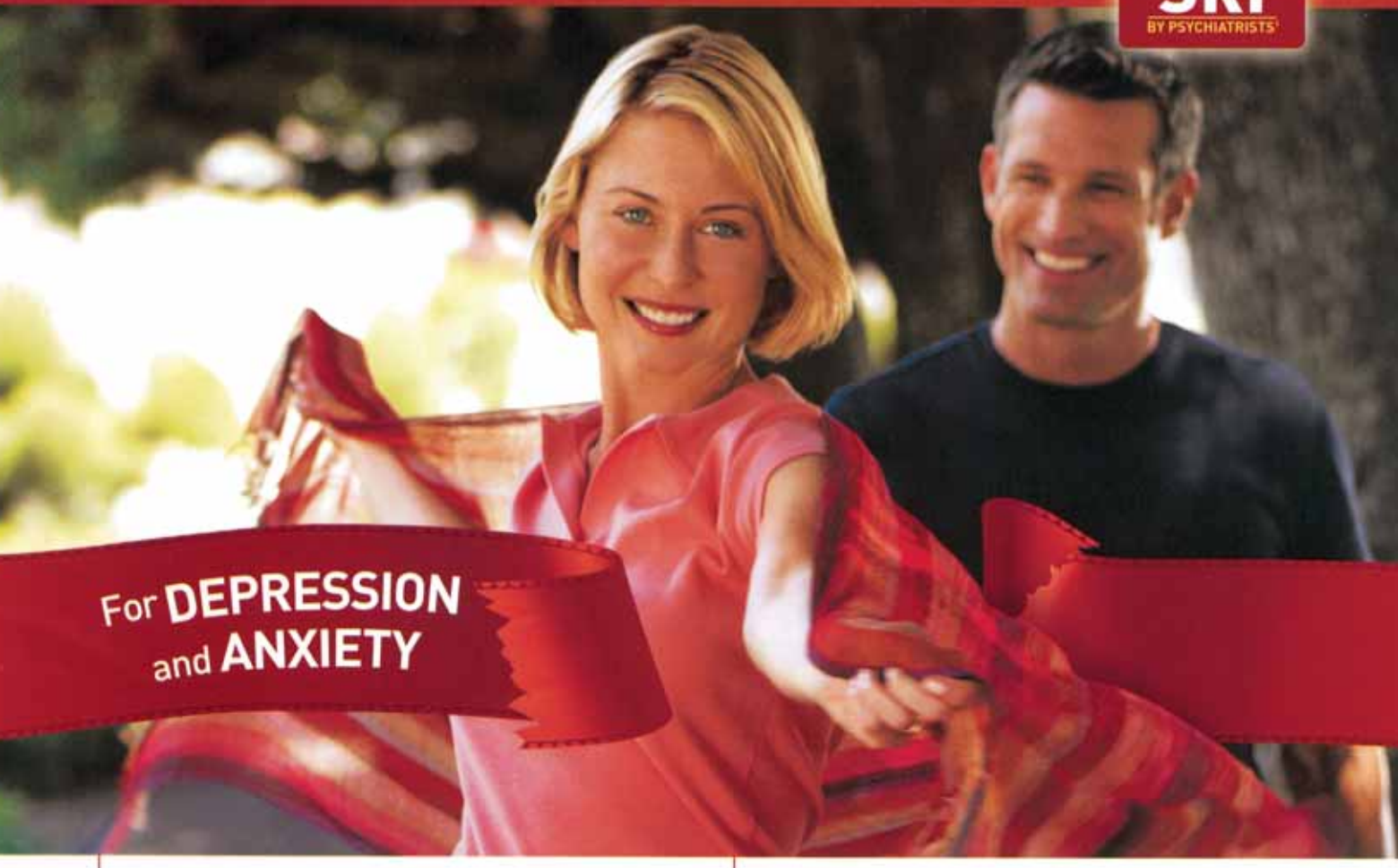
A POWERFUL SSRI that's well tolerated

#1 PRESCRIBED SRI BY PSYCHIATRISTS[1]



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

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

Lexapro escitalopram oxalate

POWER TO ENJOY LIFE™

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

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

References: 1. IMS National Prescription Audit. May 2005. **2.** Sadock BJ, Sadock VA. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins;2003:552. **3.** LEXAPRO (package insert). St Louis, Mo: Forest Pharmaceuticals, Inc.; 2005.

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

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

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

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

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

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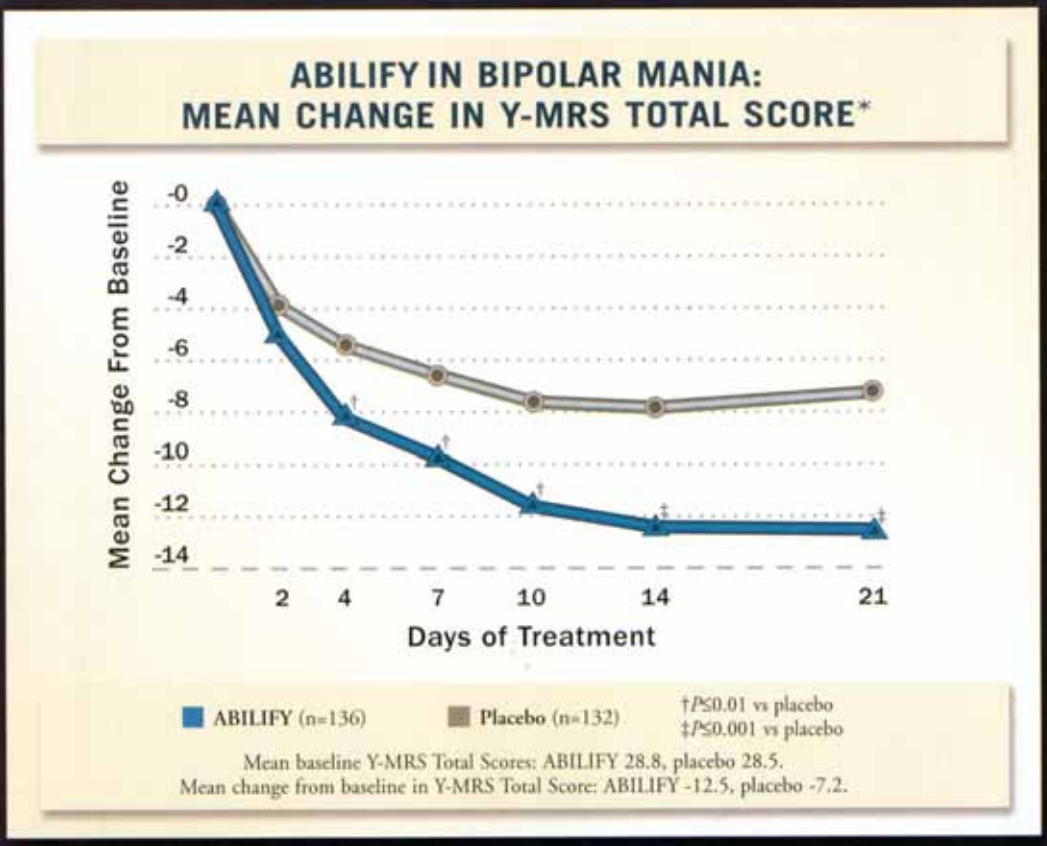
ABILIFY® (aripiprazole) efficacy looks good on paper...



Adapted from Sachs et al. *J Psychopharmacol.* 2006.

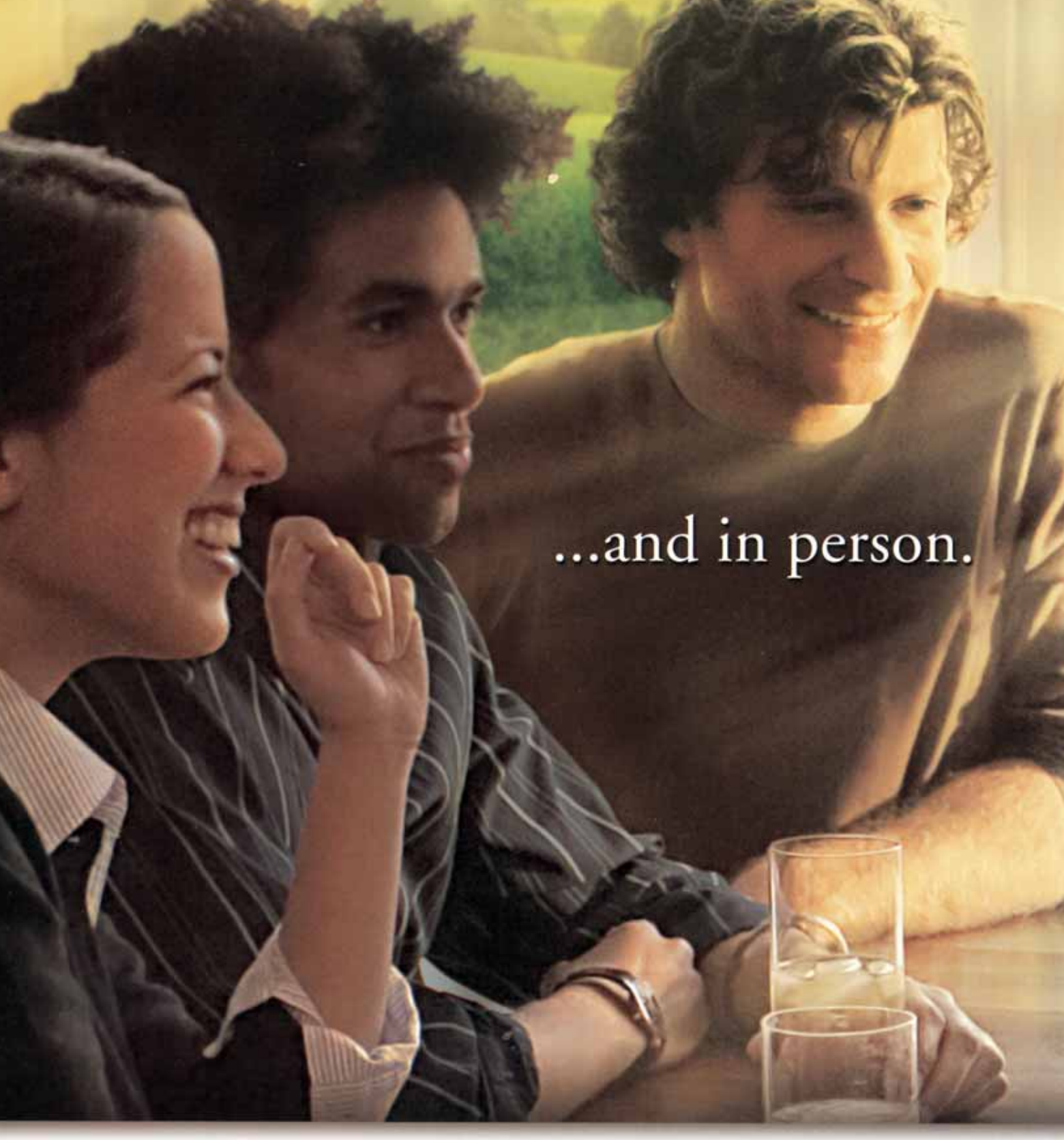
Data from a 3-week, double-blind, randomized, placebo-controlled trial in patients with **Bipolar I Disorder** experiencing acute manic or mixed episodes. Patients were randomized to receive either placebo or aripiprazole with a starting dose of 30 mg/day that could be reduced to 15 mg/day for tolerability and subsequently increased to 30 mg/day for clinical response.

* Last observation carried forward (LOCF).

Y-MRS: Young Mania Rating Scale (range 0 to 60).

ABILIFY is indicated for the treatment of acute manic and mixed episodes associated with Bipolar I Disorder.

Please see IMPORTANT SAFETY INFORMATION, including **Bolded WARNING**, and INDICATIONS on page 4.



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. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular or infectious in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Please see IMPORTANT SAFETY INFORMATION and INDICATIONS on page 4.

ABILIFY®
(aripiprazole)
TABLETS and ORAL SOLUTION 1 mg/mL

HELP ILLUMINATE THE PERSON WITHIN

IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY® (aripiprazole)

IMPORTANT SAFETY 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. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular or infectious in nature. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).
- ABILIFY is contraindicated in patients with a known **hypersensitivity** to the product.
- As with all antipsychotic medications, including ABILIFY, a rare condition referred to as **neuroleptic malignant syndrome** (NMS) has been reported. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of **tardive dyskinesia** (TD).
- **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, including a significant dose-response relationship in a fixed-dose trial. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
- **Hyperglycemia**, including some serious cases ranging from ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Patients on ABILIFY should be appropriately tested before and monitored during treatment.

ABILIFY may be associated with **orthostatic hypotension** and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

As with other antipsychotic drugs, ABILIFY should be used with caution in patients with a history of **seizures** or with conditions that lower the seizure threshold.

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

Disruption of the body's ability to reduce **core body temperature** has been attributed to antipsychotics. Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

As antipsychotics have been associated with **esophageal dysmotility and aspiration**, ABILIFY should be used cautiously in patients at risk for aspiration pneumonia.

As the possibility of a **suicide** attempt is inherent in psychotic illness and bipolar disorder, close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY (aripiprazole) should be written for the smallest quantity consistent with good patient management to reduce the risk of overdose.

Physicians should determine if a patient is **pregnant** or intends to become pregnant while taking ABILIFY. Patients should be advised not to breast-feed while taking ABILIFY.

Patients should be advised to avoid alcohol while taking ABILIFY.

Both CYP3A4 and CYP2D6 are responsible for ABILIFY metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause an increase in ABILIFY clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit ABILIFY elimination and cause increased blood levels.

Commonly observed adverse events reported with ABILIFY in 3-week bipolar mania trials at a ≥5% incidence for ABILIFY and at a rate at least twice the rate of placebo include, respectively, akathisia (15% vs 4%), constipation (13% vs 6%), and accidental injury (6% vs 3%).

Treatment-emergent adverse events reported with ABILIFY in short-term trials at an incidence ≥10% and greater than placebo, respectively, include headache (31% vs 26%), agitation (25% vs 24%), anxiety (20% vs 17%), insomnia (20% vs 15%), nausea (16% vs 12%), dyspepsia (15% vs 13%), somnolence (12% vs 8%), akathisia (12% vs 5%), lightheadedness (11% vs 8%), vomiting (11% vs 6%), and constipation (11% vs 7%).

The adverse events reported in a 26-week, double-blind schizophrenia trial comparing ABILIFY and placebo were generally consistent with those reported in the short-term, placebo-controlled schizophrenia trials, except for a higher incidence of tremor: 9% for ABILIFY vs 1% for placebo.

INDICATIONS: ABILIFY is 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*
- Acute manic and mixed episodes associated with Bipolar I Disorder
- Maintaining efficacy in patients with Bipolar I Disorder with a recent manic or mixed episode who had been stabilized and then maintained for at least 6 weeks*

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

ABILIFY is taken once daily with or without food.

Please see BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on the following pages.

New ABILIFY® DISCMELT™ (aripiprazole)

Orally Disintegrating Tablets

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Brief Summary of Prescribing Information. For complete prescribing information please consult official package circular.

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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis.

CONTRAINDICATIONS

ABILIFY (aripiprazole) 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. ABILIFY is not approved for the treatment of patients with 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 in association with administration of antipsychotic drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole treatment in the premarketing worldwide clinical database. 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.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

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

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome 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 the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. 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. In patients who do 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 of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

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 (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole 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**, and **PRECAUTIONS:** *Use in Patients with Concomitant Illness: Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease.*)

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. There have been few reports of hyperglycemia in patients treated with ABILIFY. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. 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. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include ABILIFY suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

Aripiprazole 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 ABILIFY (aripiprazole) included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on ABILIFY included: orthostatic hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%, aripiprazole 0.5%), and syncope (placebo 0.9%, aripiprazole 0.5%).

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 schizophrenia: 14% among aripiprazole-treated patients and 12% among placebo-treated patients and in bipolar mania: 3% among aripiprazole-treated patients and 2% among placebo-treated patients).

Aripiprazole 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).

Seizure

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients with schizophrenia in short-term, placebo-controlled trials. In short-term, placebo-controlled clinical trials of patients with bipolar mania, 0.3% (2/597) of aripiprazole-treated patients and 0.2% (1/436) of placebo-treated patients experienced seizures. As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that 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.

Potential for Cognitive and Motor Impairment

In short-term, placebo-controlled trials of schizophrenia, somnolence was reported in 11% of patients on ABILIFY compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% (1/926) of patients with schizophrenia on ABILIFY in short-term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar mania, somnolence was reported in 14% of patients on ABILIFY compared to 7% of patients on placebo, but did not lead to discontinuation of any patients with bipolar mania. 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. 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 the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

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. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **PRECAUTIONS**: *Use in Patients with Concomitant Illness*).

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 in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness

Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses (see **CLINICAL PHARMACOLOGY: Special Populations:** *Renal Impairment* and *Hepatic Impairment* in Full Prescribing Information) 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. Patients with these diagnoses were excluded from premarketing clinical studies.

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease: In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the treatment-emergent adverse events that were reported at an incidence of ≥3% and aripiprazole incidence at least twice that for placebo were asthenia (placebo 3%, aripiprazole 8%), somnolence (placebo 3%, aripiprazole 9%), urinary incontinence (placebo 1%, aripiprazole 5%), excessive salivation (placebo 0%, aripiprazole 4%), and lightheadedness (placebo 1%, aripiprazole 4%).

The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. 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 also **Boxed WARNING**, **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**, and **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis**.)

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY:

Interference with Cognitive and Motor Performance: Because aripiprazole may have 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 aripiprazole 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 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.

Alcohol: Patients should be advised to avoid alcohol while taking ABILIFY.

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

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

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.

Drug-Drug Interactions

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally acting drugs and alcohol. Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Potential for Other Drugs to Affect ABILIFY

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (e.g., carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Ketoconazole: Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Quinidine: Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when concomitant administration of quinidine with aripiprazole occurs. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Carbamazepine: Coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, aripiprazole dose should then be reduced.

No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions** in Full Prescribing Information).

Potential for ABILIFY (aripiprazole) to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 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. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions** in Full Prescribing Information).

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

Lifetime 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 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m^2). 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).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in 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 maximum recommended human dose [MRHD] on a 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 a 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

Pregnancy Category C

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg, however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of skeletal abnormality (fused sternebrae at 30 and 100 mg/kg) and minor skeletal variations (100 mg/kg).

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

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

Of the 7951 patients treated with aripiprazole in premarketing clinical trials, 991 (12%) were ≥65 years old and 789 (10%) were ≥75 years old. The majority (88%) of the 991 patients were diagnosed with dementia of the Alzheimer's type.

Placebo-controlled studies of 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 **Boxed WARNING**; **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**; **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis**; and **PRECAUTIONS:** *Use in Patients with Concomitant Illness*). The safety and efficacy of ABILIFY (aripiprazole) in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 7951 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5235 patient-years of exposure. A total of 2280 aripiprazole-treated patients were treated for at least 180 days and 1558 aripiprazole-treated patients had at least 1 year of exposure.

The conditions and duration of treatment with aripiprazole included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing 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. There was no attempt to use investigator causality assessments; ie, all reported events are included.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors 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 treatment, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Schizophrenia

The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which aripiprazole was administered in doses ranging from 2 to 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole- and placebo-treated patients.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

The following findings are based on a pool of 3-week, placebo-controlled, bipolar mania trials in which aripiprazole was administered at doses of 15 or 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, in patients with bipolar mania, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (11%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

Commonly observed adverse events associated with the use of aripiprazole in patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 1. There were no adverse events in the short-term trials of schizophrenia that met these criteria.

Table 1: Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

	Percentage of Patients Reporting Event	
Adverse Event	Aripiprazole (n=597)	Placebo (n=436)
Accidental Injury	6	3
Constipation	13	6
Akathisia	15	4

Adverse Events Occurring at an Incidence of 2% or More Among Aripiprazole-Treated Patients and Greater than Placebo in Short-Term, Placebo-Controlled Trials

Table 2 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 2: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials

	Percentage of Patients Reporting Event[a]	
Body System Adverse Event	Aripiprazole (n=1523)	Placebo (n=849)
Body as a Whole		
Headache	31	26
Asthenia	8	7
Accidental Injury	5	4
Peripheral Edema	2	1
Cardiovascular System		
Hypertension	2	1
Digestive System		
Nausea	16	12
Dyspepsia	15	13
Vomiting	11	6
Constipation	11	7
Musculoskeletal System		
Myalgia	4	3
Nervous System		
Agitation	25	24
Anxiety	20	17
Insomnia	20	15
Somnolence	12	8
Akathisia	12	5
Lightheadedness	11	8
Extrapyramidal Syndrome	6	4
Tremor	4	3
Increased Salivation	3	1
Respiratory System		
Pharyngitis	4	3
Rhinitis	4	3
Coughing	3	2
Special Senses		
Blurred Vision	3	1

[a] Events reported by at least 2% of patients treated with aripiprazole, except the following events, which had an incidence equal to or less than placebo: abdominal pain, back pain, dental pain, diarrhea, dry mouth, anorexia, psychosis, hypertonia, upper respiratory tract infection, rash, vaginitis[f], dysmenorrhea[f].

[f] Percentage based on gender total.

An examination of population subgroups did not reveal any clear evidence of differential adverse event incidence on the basis of age, gender, or race.

Dose-Related Adverse Events

Schizophrenia

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, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 17% vs. 12% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the bipolar mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

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%).

Table 3 provides the weight change results from a long-term (26-week), placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 3: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample

	BMI <23		BMI 23-27		BMI >27	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
Mean change from baseline (kg)	-0.5	-0.5	-0.6	-1.3	-1.5	-2.1
% with ≥7% increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

Table 4 provides the weight change results from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 4: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample

	BMI <23	BMI 23-27	BMI >27
Mean change from baseline (kg)	2.6	1.4	-1.2
% with ≥7% increase BW	30%	19%	8%

ECG Changes

Between group comparisons for a pooled analysis of placebo-controlled trials in patients with schizophrenia or bipolar mania, revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. 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.

Additional Findings Observed in Clinical Trials

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

The adverse events reported in a 26-week, double-blind trial comparing ABILIFY (aripiprazole) and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9% (13/153) for ABILIFY vs. 1% (2/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days), and were of limited duration (9/13 ≤10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for ABILIFY was 4% (34/859). A similar adverse event profile was observed in a long-term study in bipolar disorder.

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 7951 patients. All reported events are included except those already listed in Table 2, or other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent – flu syndrome, fever, chest pain, rigidity (including neck and extremity), neck pain, pelvic pain; *Infrequent* – face edema, suicide attempt, malaise, migraine, chills, photosensitivity, tightness (including abdomen, back, extremity, head, jaw, neck, and tongue), jaw pain, bloating, enlarged abdomen, chest tightness, throat pain; *Rare* – moniliasis, head heaviness, throat tightness, Mendelson's syndrome, heat stroke.

Cardiovascular System: Frequent – tachycardia (including ventricular and supraventricular), hypotension, bradycardia; *Infrequent* – palpitation, hemorrhage, heart failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris, pallor, cardiopulmonary arrest, phlebitis; *Rare* – bundle branch block, atrial flutter, vasovagal reaction, cardiomegaly, thrombophlebitis, cardiopulmonary failure.

Digestive System: Frequent – nausea and vomiting; *Infrequent* – increased appetite, dysphagia, gastroenteritis, flatulence, tooth caries, gastritis, gingivitis, gastrointestinal hemorrhage, hemorrhoids, gastroesophageal reflux, periodontal abscess, fecal incontinence, rectal hemorrhage, stomatitis, colitis, tongue edema, cholecystitis, mouth ulcer, oral moniliasis, eructation, fecal impaction, cholelithiasis; *Rare* – esophagitis, hematemesis, intestinal obstruction, gum hemorrhage, hepatitis, peptic ulcer, glossitis, melena, duodenal ulcer, cheilitis, hepatomegaly, pancreatitis.

Endocrine System: Infrequent – hypothyroidism; *Rare* – goiter, hyperthyroidism.

Hemic/Lymphatic System: Frequent – ecchymosis, anemia; *Infrequent* – hypochromic anemia, leukocytosis, leukopenia (including neutropenia), lymphadenopathy, eosinophilia, macrocytic anemia; *Rare* – thrombocythemia, thrombocytopenia, petechiae.

Metabolic and Nutritional Disorders: Frequent – weight loss, creatine phosphokinase increased, dehydration; *Infrequent* – edema, hyperglycemia, hypercholesteremia, hypokalemia, diabetes mellitus, hypoglycemia, hyperlipemia, SGPT increased, thirst, BUN increased, hyponatremia, SGOT increased, creatinine increased, cyanosis, alkaline phosphatase increased, bilirubinemia, iron deficiency anemia, hyperkalemia, hyperuricemia, obesity; *Rare* – lactic dehydrogenase increased, hypernatremia, gout, hypoglycemic reaction.

Musculoskeletal System: Frequent – muscle cramp; *Infrequent* – arthralgia, myasthenia, arthrosis, bone pain, arthritis, muscle weakness, spasm, bursitis, myopathy; *Rare* – rheumatoid arthritis, rhabdomyolysis, tendonitis, tenosynovitis.

Nervous System: Frequent – depression, nervousness, schizophrenic reaction, hallucination, hostility, confusion, paranoid reaction, suicidal thought, abnormal gait, manic reaction, delusions, abnormal dream; *Infrequent* – emotional lability, twitch, cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence, extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, panic attack, decreased libido, hypersomnia, dyskinesia, manic depressive reaction, ataxia, visual hallucination, cerebrovascular accident, hypokinesia, depersonalization, impaired memory, delirium, dysarthria, tardive dyskinesia, amnesia, hyperactivity, increased libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia, increased reflexes, akinesia, decreased consciousness, hyperesthesia, slowed thinking; *Rare* – blunted affect, euphoria, incoordination, oculogyric crisis, obsessive thought, hypotonia, buccoglossal syndrome, decreased reflexes, derealization, intracranial hemorrhage.

Respiratory System: Frequent – sinusitis, dyspnea, pneumonia, asthma; *Infrequent* – epistaxis, hiccup, laryngitis, aspiration pneumonia; *Rare* – pulmonary edema, increased sputum, pulmonary embolism, hypoxia, respiratory failure, apnea, dry nasal passages, hemoptysis.

Skin and Appendages: Frequent – skin ulcer, sweating, dry skin; *Infrequent* – pruritus, vesiculobullous rash, acne, eczema, skin discoloration, alopecia, seborrhea, psoriasis; *Rare* – maculopapular rash, exfoliative dermatitis, urticaria.

Special Senses: Frequent – conjunctivitis; *Infrequent* – ear pain, dry eye, eye pain, tinnitus, cataract, otitis media, altered taste, blepharitis, eye hemorrhage, deafness; *Rare* – diplopia, frequent blinking, ptosis, otitis externa, amblyopia, photophobia.

Urogenital System: Frequent – urinary incontinence; *Infrequent* – urinary frequency, leukorrhea, urinary retention, cystitis, hematuria, dysuria, amenorrhea, vaginal hemorrhage, abnormal ejaculation, kidney failure, vaginal moniliasis, urinary urgency, gynecomastia, kidney calculus, albuminuria, breast pain, urinary burning; *Rare* – nocturia, polyuria, menorrhagia, anorgasmy, glycosuria, cervicitis, uterus hemorrhage, female lactation, urolithiasis, priapism.

Other Events Observed During the Postmarketing Evaluation of Aripiprazole

Voluntary reports of adverse events in patients taking aripiprazole that have been received since market introduction and not listed above that may have no causal relationship with the drug include rare occurrences of allergic reaction (e.g., anaphylactic reaction, angioedema, laryngospasm, pruritus, or urticaria).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILIFY (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. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and 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. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

MedDRA terminology has been used to classify the adverse events.

Human Experience

A total of 76 cases of deliberate or accidental overdosage with aripiprazole have been reported worldwide. These include overdoses with aripiprazole alone and in combination with other substances. No fatality was reported from these cases. Of the 44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (mydriasis and feeling abnormal). The largest known acute ingestion with a known outcome involved 1080 mg of aripiprazole (36 times the maximum recommended daily dose) in a patient who fully recovered. Included in the 76 cases are 10 cases of deliberate or accidental overdosage in children (age 12 and younger) involving aripiprazole ingestions up to 195 mg with no fatalities.

Common adverse events (reported in at least 5% of all overdose cases) reported with aripiprazole overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

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.

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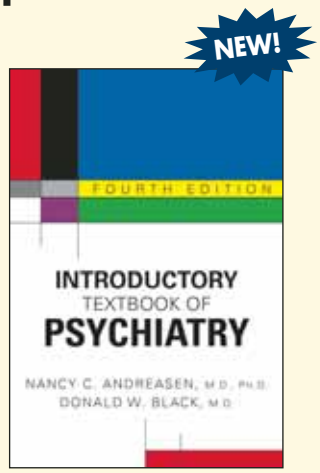

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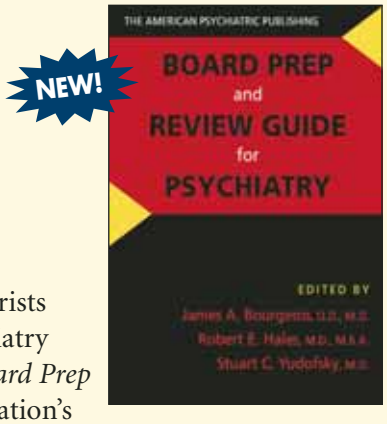

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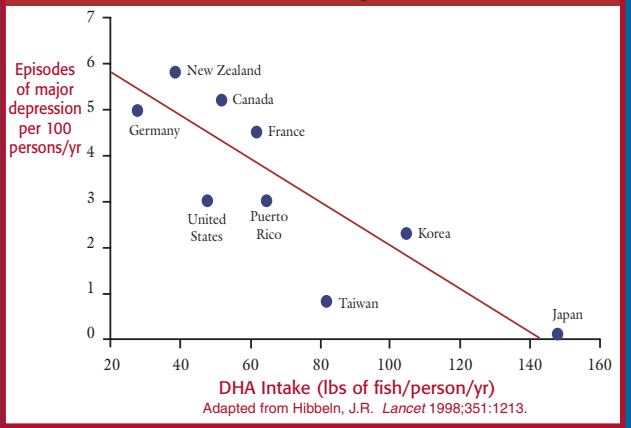

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Hibbeln, J.R. *J Affect Disord* 2002;69:15-29.

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IMPORTANT SAFETY INFORMATION

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at time of dose changes, either increases or decreases. Families and caregivers should be advised for the need for close observation and communication with the prescriber. EMSAM is not approved for use in pediatric patients (see Boxed WARNING)**

  Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking and behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials

- **To reduce the risk of hypertensive crisis, which is potentially life-threatening, foods and beverages high in tyramine must be avoided while on EMSAM 9 mg/24 hr or 12 mg/24 hr, and for 2 weeks following discontinuation of EMSAM at these doses or reducing the dose to EMSAM 6 mg/24 hr**
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- After stopping treatment with SSRIs, SNRIs, TCAs, MAOIs, mirtazapine, bupropion; meperidine and analgesics such as: tramadol, methadone, and propoxyphene; dextromethorphan; St. John's wort; and buspirone, approximately 1 week (5 weeks for fluoxetine) should elapse before starting therapy with EMSAM. At least 2 weeks should elapse after stopping EMSAM before starting therapy with buspirone or a drug that is contraindicated with EMSAM
- **Carbamazepine** and **oxcarbazepine** are contraindicated in patients taking MAO inhibitors, including EMSAM
- The use of EMSAM is contraindicated for use with **sympathomimetic amines**, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (eg, pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine)
- Patients taking EMSAM should not undergo **elective surgery requiring general anesthesia** or be given **local anesthesia** containing sympathomimetic vasoconstrictors
- EMSAM should not be used in the presence of **pheochromocytoma** since such tumors secrete pressor substances
- **Adults** with MDD or co-morbid depression in the setting of other psychiatric illness **being treated with antidepressants** should be observed for **clinical worsening and suicidality**, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases
- Risk of **bipolar disorder** should be ruled out prior to initiating antidepressant therapy. EMSAM is not approved for the treatment of bipolar depression
- Due to the potential for elevated blood pressure, the use of EMSAM with **buspirone** is not recommended
- As with other MAOIs, **postural hypotension** can occur with EMSAM therapy. Dose increases in the **elderly** should be made with caution and patients should be observed closely for postural changes in blood pressure throughout treatment
- EMSAM should be used with caution in patients with certain concomitant systemic illnesses that can produce **altered metabolism or hemodynamic responses**
- As with other psychoactive drugs, EMSAM may have the potential to **impair judgment, thinking, or motor skills**. Patients should not drive or operate hazardous machinery until they are certain EMSAM does not impair their ability to engage in such activities
- The use of **alcohol** is not recommended while taking EMSAM
- EMSAM should not be used in combination with **tyramine-containing nutritional supplements**
- EMSAM should be used in **pregnancy** only if the potential benefit justifies the potential risk to the fetus. Caution should be exercised when administering EMSAM to a nursing mother
- EMSAM is contraindicated in patients with known **hypersensitivity** to selegiline or to any component of the transdermal system
- **Treatment-emergent adverse events** in short-term clinical trials that occurred at a ≥2% incidence with EMSAM and for which the incidence was greater than placebo include: application site reaction (24% vs 12%), headache (18% vs 17%), insomnia (12% vs 7%), diarrhea (9% vs 7%), dry mouth (8% vs 6%), dyspepsia (4% vs 3%), rash (4% vs 2%), pharyngitis (3% vs 2%), and sinusitis (3% vs 1%)

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INDICATION

EMSAM is indicated for the treatment of Major Depressive Disorder (MDD).

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Suicidality in Children and Adolescents

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

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

CONTRAINDICATIONS

EMSAM is contraindicated in patients with known hypersensitivity to selegiline or to any component of the transdermal system.

EMSAM is contraindicated with selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, and paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine); tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline); bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone and propoxyphene; the antitussive agent dextromethorphan; St. John's wort; mirtazapine; and cyclobenzaprine. **EMSAM** should not be used with oral selegiline or other MAO inhibitors (MAOIs e.g., isocarboxazid, phenelzine, and tranylcypromine) (see **WARNINGS**).

Carbamazepine and oxcarbazepine are contraindicated in patients taking selegiline (see **PRECAUTIONS, Drug Interactions**).

As with other MAOIs, **EMSAM** is contraindicated for use with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine).

As with other MAOIs, patients taking **EMSAM** should not undergo elective surgery requiring general anesthesia. Also, they should not be given cocaine or local anesthesia containing sympathomimetic vasoconstrictors. **EMSAM** should be discontinued at least 10 days prior to elective surgery. If surgery is necessary sooner, benzodiazepines, mivacurium, rapacuronium, fentanyl, morphine, and codeine may be used cautiously.

As with other MAOIs, **EMSAM** is contraindicated for use in patients with pheochromocytoma.

EMSAM is an irreversible MAO inhibitor. As a class, these compounds have been associated with hypertensive crises caused by the ingestion of foods containing high amounts of tyramine. In its entirety, the data for **EMSAM** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours and 12 mg/24 hours, patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours**. (See **WARNINGS** and **PRECAUTIONS, Drug Interactions**, *Tyramine*.)

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. There has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients. Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders.

Pooled analyses of short-term placebo-controlled trials of nine antidepressant drugs (SSRIs and others) in children and adolescents with MDD, OCD, or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal behavior or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. There was considerable variation in risk among drugs, but a tendency toward an increase for almost all drugs studied. The risk of suicidality was most consistently observed in the MDD trials, but there were signals of risk arising from trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. **No suicides occurred in these trials.** It is unknown whether the suicidality risk in pediatric patients extends to longer-term use, i.e., beyond several months. It is also unknown whether the suicidality risk extends to adults.

All pediatric patients being treated with antidepressants for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

Adults with MDD or co-morbid depression in the setting of other psychiatric illness being treated with antidepressants should be observed similarly for clinical worsening and suicidality, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

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

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

Families and caregivers of pediatric patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for **EMSAM** should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose. Families and caregivers of adults being treated for depression should be similarly advised.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that **EMSAM** is not approved for use in treating bipolar depression.

Hypertensive Crisis

EMSAM is an irreversible MAO inhibitor. MAO is important in the catabolism of dietary amines (e.g., tyramine). In this regard, significant inhibition of intestinal MAO-A activity can impose a cardiovascular safety risk following the ingestion of tyramine-rich foods. As a class, MAOIs have been associated with hypertensive crises caused by the ingestion of foods with a high concentration of tyramine.

Hypertensive crises, which in some cases may be fatal, are characterized by some or all of the following symptoms: occipital headache which may radiate frontally, palpitation, neck stiffness or soreness, nausea, vomiting, sweating (sometimes with fever and sometimes with cold, clammy skin), dilated pupils, and photophobia. Either tachycardia or bradycardia may be present and can be associated with constricting chest pain. Intracranial bleeding has been reported in association with the increase in blood pressure. Patients should be instructed as to the signs and symptoms of severe hypertension and advised to seek immediate medical attention if these signs or symptoms are present.

In 6 of the 7 clinical studies conducted with **EMSAM** at doses of 6 mg/24 hours–12 mg/24 hours, patients were not limited to a modified diet typically associated with this class of compounds. Although no hypertensive crises were reported as part of the safety assessment, the likelihood of developing this reaction cannot be fully determined since the amount of tyramine typically consumed during the course of treatment is not known and blood pressure was not continuously monitored.

To further define the likelihood of hypertensive crises with use of **EMSAM** (selegiline transdermal system), several Phase I tyramine challenge studies were conducted both with and without food (see **PRECAUTIONS, Drug Interactions**, *Tyramine*). In its entirety, the data for **EMSAM** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours, and the results from the Phase I tyramine challenge study in fed volunteers administered **EMSAM** 12 mg/24 hours (see **PRECAUTIONS, Drug Interactions**, *Tyramine*), patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours**.

If a hypertensive crisis occurs, **EMSAM** should be discontinued immediately and therapy to lower blood pressure should be instituted immediately. Phentolamine 5 mg or labetalol 20 mg administered slowly intravenously is recommended therapy to control hypertension. Alternately, nitroprusside delivered by continuous intravenous infusion may be used. Fever should be managed by means of external cooling. Patients must be closely monitored until symptoms have stabilized.

Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours

The following foods and beverages should be avoided beginning on the first day of **EMSAM** 9 mg/24 hours or 12 mg/24 hours treatment and should continue to be avoided for 2 weeks after a dose reduction to **EMSAM** 6 mg/24 hours or following the discontinuation of **EMSAM** 9 mg/24 hours or 12 mg/24 hours.

Food and beverages to avoid and those which are acceptable[1]:

Class of Food and Beverage	Tyramine-Rich Foods and Beverages to Avoid	Acceptable Foods, Containing No or Little Tyramine
Meat, Poultry and Fish	Air dried, aged and fermented meats, sausages and salamis (including cacciatore, hard salami and mortadella); pickled herring; and any spoiled or improperly stored meat, poultry and fish (e.g., foods that have undergone changes in coloration, odor, or become moldy); spoiled or improperly stored animal livers	Fresh meat, poultry and fish, including fresh processed meats (e.g., lunch meats, hot dogs, breakfast sausage, and cooked sliced ham)
Vegetables	Broad bean pods (fava bean pods)	All other vegetables
Dairy	Aged cheeses	Processed cheeses, mozzarella, ricotta cheese, cottage cheese and yogurt
Beverages	All varieties of tap beer and beers that have not been pasteurized so as to allow for ongoing fermentation	As with other antidepressants, concomitant use of alcohol with **EMSAM** is not recommended (Bottled and canned beers and wines contain little or no tyramine.)
Miscellaneous	Concentrated yeast extract (e.g., Marmite), sauerkraut, most soybean products (including soy sauce and tofu), OTC supplements containing tyramine	Brewer's yeast, baker's yeast, soy milk, commercial chain-restaurant pizzas prepared with cheeses low in tyramine

[1] Adapted from K. I. Shulman, S. E. Walker. *Psychiatric Annals*. 2001; 31:378-384.

Use With Other Drugs Affecting Monoamine Activity

Serious, sometimes fatal, central nervous system (CNS) toxicity referred to as the "serotonin syndrome" has been reported with the combination of non-selective MAOIs with certain other drugs, including tricyclic or selective serotonin reuptake inhibitor antidepressants, amphetamines, meperidine, or pentazocine. Serotonin syndrome is characterized by signs and symptoms that may include hyperthermia, rigidity, myoclonus, autonomic instability with rapid fluctuations of the vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Similar less severe syndromes have been reported in a few patients receiving a combination of oral selegiline with one of these agents.

Therefore, **EMSAM** should not be used in combination with selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine); dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine); tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline); oral selegiline or other MAOIs (e.g., isocarboxazid, phenelzine, and tranylcypromine); mirtazapine; bupropion hydrochloride; meperidine and analgesic agents such as tramadol, methadone, and propoxyphene; the antitussive agent dextromethorphan; or St. John's wort because of the risk of life-threatening adverse reactions. Also, **EMSAM** should not be used with sympathomimetic amines, including amphetamines as well as cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine, and ephedrine). (See **CONTRAINDICATIONS**.)

Concomitant use of **EMSAM** with buspirone hydrochloride is not advised since several cases of elevated blood pressure have been reported in patients taking MAOIs who were then given buspirone HCl.

After stopping treatment with SSRIs; SNRIs; TCAs; MAOIs; meperidine and analgesics such as tramadol, methadone, and propoxyphene; dextromethorphan; St. John's wort; mirtazapine; bupropion HCl; or buspirone HCl, a time period equal to 4-5 half-lives (approximately 1 week) of the drug or any active metabolite should elapse before starting therapy with **EMSAM**. Because of the long half-life of fluoxetine and its active metabolite, at least 5 weeks should elapse between discontinuation of fluoxetine and initiation of treatment with **EMSAM**. At least 2 weeks should elapse after stopping **EMSAM** before starting therapy with buspirone HCl or a drug that is contraindicated with **EMSAM**.

PRECAUTIONS

General

Hypotension: As with other MAOIs, postural hypotension, sometimes with orthostatic symptoms, can occur with **EMSAM** therapy. In short-term, placebo-controlled depression studies, the incidence of orthostatic hypotension (i.e., a decrease of 10 mmHg or greater in mean blood pressure when changing position from supine or sitting to standing) was 9.8% in **EMSAM**-treated patients and 6.7% in placebo-treated patients. It is recommended that elderly patients treated with **EMSAM** be closely observed for postural changes in blood pressure throughout treatment. Dose increases should be made cautiously in patients with pre-existing orthostasis. Postural hypotension may be relieved by having the patient recline until the symptoms have abated. Patients should be cautioned to change positions gradually. Patients displaying orthostatic symptoms should have appropriate dosage adjustments as warranted.

Activation of Mania/Hypomania: During Phase III trials, a manic reaction occurred in 8/2036 (0.4%) patients treated with **EMSAM**. Activation of mania/hypomania can occur in a small proportion of patients with major affective disorder treated with other marketed antidepressants. As with all antidepressants, **EMSAM** should be used cautiously in patients with a history of mania.

Use in Patients With Concomitant Illness: Clinical experience with **EMSAM** in patients with certain concomitant systemic illnesses is limited. Caution is advised when using **EMSAM** in patients with disorders or conditions that can produce altered metabolism or hemodynamic responses.

EMSAM has not been systematically evaluated in patients with a history of recent myocardial infarction or unstable heart disease. Such patients were generally excluded from clinical studies during the product's premarketing testing.

No ECG abnormalities attributable to **EMSAM** were observed in clinical trials.

Although studies of phenylpropanolamine and pseudoephedrine did not reveal pharmacokinetic drug interactions with **EMSAM**, it is prudent to avoid the concomitant use of sympathomimetic agents, such as some decongestants.

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 **EMSAM** and should counsel them in its appropriate use. A patient **Medication Guide About Using Antidepressants in Children and Teenagers** is available for **EMSAM**. 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 reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking **EMSAM**.

Clinical Worsening and Suicide Risk

Patients, their families and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment or when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly change in the medication.

General

Patients should be advised not to use oral selegiline while on **EMSAM** therapy.

Patients should be advised not to use carbamazepine or oxcarbazepine while on **EMSAM** therapy.

Patients should be advised not to use meperidine and analgesic agents such as tramadol, methadone, and propoxyphene.

Patients should be advised not to use sympathomimetic agents while on **EMSAM** therapy.

Patients should be advised not to use selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine, and St. John's wort), dual serotonin and norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine), tricyclic antidepressants (TCAs, e.g., imipramine and amitriptyline), mirtazapine, oral selegiline or other MAOIs (e.g., isocarboxazid, phenelzine, and tranylcypromine), bupropion hydrochloride or buspirone hydrochloride while on **EMSAM** (selegiline transdermal system) therapy.

EMSAM has not been shown to impair psychomotor performance; however, any psychoactive drug may potentially impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that **EMSAM** therapy does not impair their ability to engage in such activities.

Patients should be told that, although **EMSAM** has not been shown to increase the impairment of mental and motor skills caused by alcohol, the concomitant use of **EMSAM** and alcohol in depressed patients is not recommended.

Patients should be advised to notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, including herbals, because of the potential for drug interactions. Patients should also be advised to avoid tyramine-containing nutritional supplements and any cough medicine containing dextromethorphan.

Patients should be advised to use **EMSAM** exactly as prescribed. The need for dietary modifications at higher doses should be explained, and a brief description of hypertensive crisis provided. Rare hypertensive reactions with oral selegiline at doses recommended for Parkinson's disease and associated with dietary influences have been reported. The clinical relevance to **EMSAM** is unknown.

Patients should be advised that certain tyramine-rich foods and beverages should be avoided while on **EMSAM** 9 mg/24 hours or **EMSAM** 12 mg/24 hours, and for 2 weeks following discontinuation of **EMSAM** at these doses (see **CONTRAINDICATIONS** and **WARNINGS**).

Patients should be instructed to immediately report the occurrence of the following acute symptoms: severe headache, neck stiffness, heart racing or palpitations, or other sudden or unusual symptoms.

Patients should be advised to avoid exposing the **EMSAM** application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight since heat may result in an increase in the amount of selegiline absorbed from the **EMSAM** patch and produce elevated serum levels of selegiline.

Patients should be advised to change position gradually if lightheaded, faint, or dizzy while on **EMSAM** therapy.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during **EMSAM** therapy.

Patients should be advised to notify their physician if they are breast-feeding an infant.

While patients may notice improvement with **EMSAM** therapy in 1 to several weeks, they should be advised of the importance of continuing drug treatment as directed.

Patients should be advised not to cut the **EMSAM** system into smaller portions.

For instructions on how to use **EMSAM**, see **DOSAGE AND ADMINISTRATION, How to Use EMSAM.**

Drug Interactions

The potential for drug interactions between **EMSAM** and a variety of drugs was examined in several human studies. Drug interaction studies described below were conducted with **EMSAM** 6 mg/24 hours. Although no differences are expected, drug interaction studies have not been conducted at higher doses (see *In vitro* Metabolism in Full Prescribing Information). In all of the studies described below, no drug-related adverse events were noted that required discontinuation of any subjects. Further, the incidence and nature of the adverse events were consistent with those known for selegiline or the test agent.

Alcohol: The pharmacokinetics and pharmacodynamics of alcohol (0.75 mg/kg) alone or in combination with **EMSAM** 6 mg/24 hours for 7 days of treatment was examined in 16 healthy volunteers. No clinically significant differences were observed in the pharmacokinetics or pharmacodynamics of alcohol or the pharmacokinetics of selegiline during co-administration. Although **EMSAM** has not been shown to increase the impairment of mental and motor skills caused by alcohol (0.75 mg/kg) and failed to alter the pharmacokinetic properties of alcohol, patients should be advised that the use of alcohol is not recommended while taking **EMSAM**.

Alprazolam: In subjects who had received **EMSAM** 6 mg/24 hours for 7 days, co-administration with alprazolam (15 mg/day), a CYP3A4/5 substrate, did not affect the pharmacokinetics of either selegiline or alprazolam.

Carbamazepine: Carbamazepine is an enzyme inducer and typically causes decreases in drug exposure; however, slightly increased levels of selegiline and its metabolites were seen after single application of **EMSAM** 6 mg/24 hours in subjects who had received carbamazepine (400 mg/day) for 14 days. Changes in plasma selegiline concentrations were nearly two-fold, and variable across the subject population. The clinical relevance of these observations is unknown. Carbamazepine is contraindicated with MAOIs, including selegiline (see **CONTRAINDICATIONS**).

Ibuprofen: In subjects who had received **EMSAM** 6 mg/24 hours for 11 days, combined administration with the CYP2C9 substrate ibuprofen (800 mg single dose) did not affect the pharmacokinetics of either selegiline or ibuprofen.

Ketoconazole: Seven-day treatment with ketoconazole (200 mg/day), a potent inhibitor of CYP3A4, did not affect the steady-state pharmacokinetics of selegiline in subjects who received **EMSAM** 6 mg/24 hours for 7 days and no differences in the pharmacokinetics of ketoconazole were observed.

Levothyroxine: In healthy subjects who had received **EMSAM** 6 mg/24 hours for 10 days, single dose administration with levothyroxine (150 µg) did not alter the pharmacokinetics of either selegiline or levothyroxine (as judged by T_3 and T_4 plasma levels).

Olanzapine: In subjects who had received **EMSAM** 6 mg/24 hours for 10 days, co-administration with olanzapine, a substrate for CYP1A2, CYP2D6, and possibly CYP2A6, did not affect the pharmacokinetics of either selegiline or olanzapine.

Phenylpropanolamine (PPA): In subjects who had received **EMSAM** 6 mg/24 hours for 9 days, co-administration with PPA (25 mg every 4 hours for 24 hours) did not affect the pharmacokinetics of PPA. There was a higher incidence of significant blood pressure elevations with the co-administration of **EMSAM** and PPA than with PPA alone, suggesting a possible pharmacodynamic interaction. It is prudent to avoid the concomitant use of sympathomimetic agents with **EMSAM**.

Pseudoephedrine: **EMSAM** 6 mg/24 hours for 10 days, co-administered with pseudoephedrine (60 mg, 3 times a day) did not affect the pharmacokinetics of pseudoephedrine. The effect of pseudoephedrine on **EMSAM** was not examined. There were no clinically significant changes in blood pressure during pseudoephedrine administration alone, or in combination with **EMSAM**. Nonetheless, it is prudent to avoid the concomitant use of sympathomimetic agents with **EMSAM**.

Risperidone: In subjects who had received **EMSAM** 6 mg/24 hours for 10 days, co-administration with risperidone (2 mg per day for 7 days), a substrate for CYP2D6, did not affect the pharmacokinetics of either selegiline or risperidone.

Tyramine: Selegiline (the drug substance of **EMSAM**) is an irreversible inhibitor of monoamine oxidase (MAO), a ubiquitous intracellular enzyme. MAO exists as two isoenzymes, referred to as MAO-A and MAO-B. Selegiline shows greater affinity for MAO-B; however, as selegiline concentration increases, this selectivity is lost with resulting dose-related inhibition of MAO-A. Intestinal MAO is predominantly type A, while in the brain both isoenzymes exist.

MAO plays a vital physiological role in terminating the biological activity of both endogenous and exogenous amines. In addition to their role in the catabolism of monoamines in the CNS, MAOs are also important in the catabolism of exogenous amines found in a variety of foods and drugs. MAO in the gastrointestinal tract (primarily type A) provides protection from exogenous amines with vasopressor actions, such as tyramine, which if absorbed intact can cause a hypertensive crisis, the so-called "cheese reaction." If a large amount of tyramine is absorbed systemically, it is taken up by adrenergic neurons and causes norepinephrine release from neuronal storage sites with resultant elevation of blood pressure. While most foods contain negligible amounts or no tyramine, a few food products (see **WARNINGS**) may contain large amounts of tyramine that represent a potential risk for patients with significant inhibition of intestinal MAO-A resulting from administration of MAOIs. Tyramine-containing nutritional supplements should be avoided by patients taking **EMSAM**.

Animal studies have indicated the transdermal administration of selegiline via **EMSAM** 6 mg/24 hours allows for critical levels of MAO inhibition to be achieved in the brain while avoiding levels of gastrointestinal inhibition. To further define the risk of hypertensive crises with use of **EMSAM**, several Phase I tyramine challenge studies were conducted both with and without food.

Fourteen tyramine challenge studies including 214 healthy subjects (age range 18-65; 31 subjects >50 years of age) were conducted to determine the pressor effects of oral tyramine with concurrent **EMSAM** treatment (6 mg/24 hours–12 mg/24 hours), measured as the dose of tyramine required to raise systolic blood pressure by 30 mmHg (TYR30). Studies were conducted with and without concomitant administration of food. Studies conducted with food are most relevant to clinical practice since tyramine typically will be consumed in food. A high-tyramine meal is considered to contain up to 40 mg of tyramine.

One study using a crossover design in 13 subjects investigated tyramine pressor doses (TYR30) after administration of **EMSAM** 6 mg/24 hours and oral selegiline (5 mg twice daily) for 9 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 338 mg and 385 mg in subjects treated with **EMSAM** and oral selegiline, respectively.

Another study using a crossover design in 10 subjects investigated tyramine pressor doses after administration of **EMSAM** 6 mg/24 hours or tranylcypromine 30 mg/day for 10 days. Mean pressor doses (TYR30) of tyramine capsules administered without food were 270 mg in subjects treated with **EMSAM** 6 mg/24 hours and 10 mg in subjects treated with tranylcypromine.

In a third crossover study, tyramine without food was administered to 12 subjects. The mean tyramine pressor doses (TYR30) after administration of **EMSAM** 6 mg/24 hours for 9 and 33 days were 292 mg and 204 mg, respectively. The lowest pressor dose was 50 mg in one subject in the 33-day group.

Tyramine pressor doses were also studied in 11 subjects after extended treatment with **EMSAM** 12 mg/24 hours. At 30, 60, and 90 days, the mean pressor doses (TYR30) of tyramine administered without food were 95 mg, 72 mg, and 88 mg, respectively. The lowest pressor dose without food was 25 mg in 3 subjects at day 30 while on **EMSAM** 12 mg/24 hours. Eight subjects from this study, with a mean tyramine pressor dose of 64 mg at 90 days, were subsequently administered tyramine with food, resulting in a mean pressor dose of 172 mg (2.7 times the mean pressor dose observed without food, $p < 0.003$).

With the exception of one study (N=153), the Phase III clinical development program was conducted without requiring a modified diet (N=2553, 1606 at 6 mg/24 hours, and 947 at 9 mg/24 hours or 12 mg/24 hours). No hypertensive crises were reported in any patient receiving **EMSAM** (selegiline transdermal system).

In its entirety, the data for **EMSAM** 6 mg/24 hours support the recommendation that a modified diet is not required at this dose. Due to the more limited data available for **EMSAM** 9 mg/24 hours and 12 mg/24 hours, patients receiving these doses should follow **Dietary Modifications Required for Patients Taking EMSAM 9 mg/24 hours and 12 mg/24 hours**. (See **WARNINGS**.)

Warfarin: Warfarin is a substrate for CYP2C9 and CYP3A4 metabolism pathways. In healthy volunteers titrated with Coumadin® (warfarin sodium) to clinical levels of anticoagulation (INR of 1.5 to 2), co-administration with **EMSAM** 6 mg/24 hours for 7 days did not affect the pharmacokinetics of the individual warfarin enantiomers. **EMSAM** did not alter the clinical pharmacodynamic effects of warfarin as measured by INR, Factor VII or Factor X levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In an oral carcinogenicity study in rats, selegiline given in the diet for 104 weeks was not carcinogenic up to the highest evaluable dose tested (3.5 mg/kg/day, which is 3 times the oral maximum recommended human dose on a mg/m² basis).

Carcinogenicity studies have not been conducted with transdermal administration of selegiline.

Mutagenesis: Selegiline induced mutations and chromosomal damage when tested in the *in vitro* mouse lymphoma assay with and without metabolic activation. Selegiline was negative in the Ames assay, the *in vitro* mammalian chromosome aberration assay in human lymphocytes, and the *in vivo* oral mouse micronucleus assay.

Impairment of Fertility: A mating and fertility study was conducted in male and female rats at transdermal doses of 10, 30, and 75 mg/kg/day of selegiline (8, 24 and 60 times the maximum recommended human dose of **EMSAM** [12 mg/ 24 hours] on a mg/m² basis). Slight decreases in sperm concentration and total sperm count were observed at the high dose; however, no significant adverse effects on fertility or reproductive performance were observed.

Teratogenic Effects - Pregnancy Category C

In an embryofetal development study in rats, dams were treated with transdermal selegiline during the period of organogenesis at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the maximum recommended human dose [MRHD] of **EMSAM** [12 mg/24 hours] on a mg/m² basis). At the highest dose there was a decrease in fetal weight and slight increases in malformations, delayed ossification (also seen at the mid dose), and embryofetal post-implantation lethality. Concentrations of selegiline and its metabolites in fetal plasma were generally similar to those in maternal plasma. In an *oral* embryofetal development study in rats, a decrease in fetal weight occurred at the highest dose tested (36 mg/kg; no-effect dose 12 mg/kg); no increase in malformations was seen.

In an embryofetal development study in rabbits, dams were treated with transdermal selegiline during the period of organogenesis at doses of 2.5, 10, and 40 mg/kg/day (4, 16, and 64 times the MRHD on a mg/m² basis). A slight increase in visceral malformations was seen at the high dose. In an *oral* embryofetal development study in rabbits, increases in total resorptions and post-implantation loss, and a decrease in the number of live fetuses per dam, occurred at the highest dose tested (50 mg/kg; no-effect dose 25 mg/kg).

In a prenatal and postnatal development study in rats, dams were treated with transdermal selegiline at doses of 10, 30, and 75 mg/kg/day (8, 24, and 60 times the MRHD on a mg/m² basis) on days 6-21 of gestation and days 1-21 of the lactation period. An increase in post-implantation loss was seen at the mid and high doses, and an increase in stillborn pups was seen at the high dose. Decreases in pup weight (throughout lactation and post-weaning periods) and survival (throughout lactation period), retarded pup physical development, and pup epididymal and testicular hypoplasia, were seen at the mid and high doses. Retarded neurobehavioral and sexual development was seen at all doses. Adverse effects on pup reproductive performance, as evidenced by decreases in implantations and litter size, were seen at the high dose. These findings suggest persistent effects on the offspring of treated dams. A no-effect dose was not established for developmental toxicity. In this study concentrations of selegiline and its metabolites in milk were ~ 15 and 5 times, respectively, the concentrations in plasma, indicating that the pups were directly dosed during the lactation period.

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

Labor and Delivery

The effect of **EMSAM** on labor and delivery in humans is unknown.

Nursing Mothers

In a prenatal and postnatal study of transdermal selegiline in rats, selegiline and metabolites were excreted into the milk of lactating rats. The levels of selegiline and metabolites in milk were approximately 15 and 5 times, respectively, steady-state levels of selegiline and metabolites in maternal plasma. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised administering **EMSAM** to a nursing mother.

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 **EMSAM** in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use

One hundred ninety-eight (198) elderly (≥65 years of age) patients participated in clinical studies with **EMSAM** 6 mg/24 hours to 12 mg/24 hours. There were no overall differences in effectiveness between elderly and younger patients. In short-term, placebo-controlled depression trials, patients age 50 and older appeared to be at higher risk for rash (4.4% **EMSAM** versus 0% placebo) than younger patients (3.4% **EMSAM** versus 2.4% placebo).

ADVERSE REACTIONS

The premarketing development program for **EMSAM** included selegiline exposures in patients and/or normal subjects from two different groups of studies: 702 healthy subjects in clinical pharmacology/pharmacokinetics studies and 2036 exposures from patients in controlled and uncontrolled major depressive disorder clinical trials. The conditions and duration of treatment with **EMSAM** varied and included double-blind, open-label, fixed-dose, and dose titration studies of short-term and longer-term exposures. Safety was assessed by monitoring adverse events, physical examinations, vital signs, body weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators. In the tables and tabulations that follow, standard 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 Observed in Short-Term, Placebo-Controlled Trials

Adverse Events Associated with Discontinuation of Treatment: Among 817 depressed patients who received **EMSAM** at doses of either 3 mg/24 hours (151 patients), 6 mg/24 hours (550 patients) or 6 mg/24 hours, 9 mg/24 hours, and 12 mg/24 hours (116 patients) in placebo-controlled trials of up to 8 weeks in duration, 7.1% discontinued treatment due to an adverse event as compared with 3.6% of 668 patients receiving placebo. The only adverse event associated with discontinuation, in at least 1% of **EMSAM**-treated patients at a rate at least twice that of placebo, was application site reaction (2% **EMSAM** vs. 0% placebo).

Adverse Events Occurring at an Incidence of 2% or More Among **EMSAM***-Treated Patients:* Table 1 enumerates adverse events that occurred at an incidence of 2% or more (rounded to the nearest percent) among 817 depressed patients who received **EMSAM** in doses ranging from 3 to 12 mg/24 hours in placebo-controlled trials of up to 8 weeks in duration. Events included are those occurring in 2% or more of patients treated with **EMSAM** and for which the incidence in patients treated with **EMSAM** was greater than the incidence in placebo-treated patients.

Only one adverse event was associated with a reporting of at least 5% in the **EMSAM** group, and a rate at least twice that in the placebo group, in the pool of short-term, placebo-controlled studies: application site reactions (see *Application Site Reactions*, below). In one such study which utilized higher mean doses of **EMSAM** than that in the entire study pool, the following events met these criteria: application site reactions, insomnia, diarrhea, and pharyngitis.

These figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical 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 physicians 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. Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder With EMSAM (selegiline transdermal system)[1]

Body System/Preferred Term	EMSAM (N=817)	Placebo (N=668)
	(% of Patients Reporting Event)	
Body as a Whole		
Headache	18	17
Digestive		
Diarrhea	9	7
Dyspepsia	4	3
Nervous		
Insomnia	12	7
Dry Mouth	8	6
Respiratory		
Pharyngitis	3	2
Sinusitis	3	1
Skin		
Application Site Reaction	24	12
Rash	4	2

[1] Events reported by at least 2% of patients ≥ treated with **EMSAM** are included, except the following events which had an incidence on placebo treatment ≥ to **EMSAM**: infection, nausea, dizziness, pain, abdominal pain, nervousness, back pain, asthenia, anxiety, flu syndrome, accidental injury, somnolence, rhinitis, and palpitations.

Application Site Reactions: In the pool of short-term, placebo-controlled major depressive disorder studies, application site reactions (ASRs) were reported in 24% of **EMSAM**-treated patients and 12% of placebo-treated patients. Most ASRs were mild or moderate in severity. None were considered serious. ASRs led to dropout in 2% of **EMSAM**-treated patients and no placebo-treated patients.

In one such study which utilized higher mean doses of **EMSAM**, ASRs were reported in 40% of **EMSAM**-treated patients and 20% of placebo-treated patients. Most of the ASRs in this study were described as erythema and most resolved spontaneously, requiring no treatment. When treatment was administered, it most commonly consisted of dermatological preparations of corticosteroids.

Male and Female Sexual Dysfunction with MAO Inhibitors: 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, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 2 shows that the incidence rates of sexual side effects in patients with major depressive disorder are comparable to the placebo rates in placebo-controlled trials.

Table 2. Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials With EMSAM

Adverse Event	EMSAM	Placebo
	IN MALES ONLY	
	(N=304)	(N=256)
Abnormal Ejaculation	1.0%	0.0%
Decreased Libido	0.7%	0.0%
Impotence	0.7%	0.4%
Anorgasmia	0.2%	0.0%
	IN FEMALES ONLY	
	(N=513)	(N=412)
Decreased Libido	0.0%	0.2%

There are no adequately designed studies examining sexual dysfunction with **EMSAM** treatment.

Vital Sign Changes: **EMSAM** and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. In the pool of short-term, placebo-controlled major depressive disorder studies, 3.0% of **EMSAM**-treated patients and 1.5% of placebo-treated patients experienced a low systolic blood pressure, defined as a reading less than or equal to 90 mmHg with a change from baseline of at least 20 mmHg. In one study which utilized higher mean doses of **EMSAM**, 6.2% of **EMSAM**-treated patients and no placebo-treated patients experienced a low standing systolic blood pressure by these criteria.

In the pool of short-term major depressive disorder trials, 9.8% of **EMSAM**-treated patients and 6.7% of placebo-treated patients experienced a notable orthostatic change in blood pressure, defined as a decrease of at least 10 mmHg in mean blood pressure with postural change.

Weight Changes: In placebo-controlled studies (6 - 8 weeks), the incidence of patients who experienced ≥5% weight gain or weight loss is shown in Table 3.

Table 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials With EMSAM

Weight Change	EMSAM	Placebo
	(N=757)	(N=614)
Gained ≥ 5%	2.1%	2.4%
Lost ≥ 5%	5.0%	2.8%

In these trials, the mean change in body weight among **EMSAM**-treated patients was -1.2 lbs compared to +0.3 lbs in placebo-treated patients.

Laboratory Changes: **EMSAM** and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with **EMSAM**.

ECG Changes: Electrocardiograms (ECGs) from **EMSAM** (N=817) and placebo (N=668) groups in controlled studies were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for clinically significant changes from baseline in these variables.

No clinically meaningful changes in ECG parameters from baseline to final visit were observed for patients in controlled studies.

Other Events Observed During the Premarketing Evaluation of EMSAM

During the premarketing assessment in major depressive disorder, **EMSAM** was administered to 2036 patients in Phase III studies. The conditions and duration of exposure to **EMSAM** varied and included double-blind and open-label studies.

In the tabulations that follow, reported adverse events were classified using a standard COSTART–based dictionary terminology. All reported adverse events are included except those already listed in Table 1 or elsewhere in labeling, and those events occurring in only one patient. It is important to emphasize that although the events occurred during treatment with **EMSAM**, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: *Frequent:* Chest pain, neck pain. *Infrequent:* Bacterial infection, fever, cyst, fungal infection, chills, viral infection, suicide attempt, neck rigidity, pelvic pain, photosensitivity reaction, face edema, flank pain, hernia, intentional injury, neoplasm, generalized edema, overdose. *Rare:* Body odor, halitosis, heat stroke, parasitic infection, malaise, moniliasis.

Cardiovascular System: *Frequent:* Hypertension. *Infrequent:* Vasodilatation, tachycardia, migraine, syncope, atrial fibrillation, peripheral vascular disorder. *Rare:* Myocardial infarct.

Digestive System: *Frequent:* Constipation, flatulence, anorexia, gastroenteritis, vomiting. *Infrequent:* Increased appetite, thirst, periodontal abscess, eructation, gastritis, colitis, dysphagia, tongue edema, glossitis, increased salivation, abnormal liver function tests, melena, tongue disorder, tooth caries. *Rare:* GI neoplasia, rectal hemorrhage.

Hemic and Lymphatic System: *Frequent:* Ecchymosis. *Infrequent:* Anemia, lymphadenopathy. *Rare:* Leukocytosis, leukopenia, petechia.

Metabolic and Nutritional: *Frequent:* Peripheral edema. *Infrequent:* Hyperglycemia, increased SGPT, edema, hypercholesteremia, increased SGOT, dehydration, alcohol intolerance, hyponatremia, increased lactic dehydrogenase. *Rare:* Increased alkaline phosphatase, bilirubinemia, hypoglycemic reaction.

Musculoskeletal System: *Frequent:* Myalgia, pathological fracture. *Infrequent:* Arthralgia, generalized spasm, arthritis, myasthenia, arthrosis, tenosynovitis. *Rare:* Osteoporosis.

Nervous System: *Frequent:* Agitation, paresthesia, thinking abnormal, amnesia. *Infrequent:* Leg cramps, tremor, vertigo, hypertonia, twitching, emotional lability, confusion, manic reaction, depersonalization, hyperkinesias, hostility, myoclonus, circumoral paresthesia, hyperesthesia, increased libido, euphoria, neurosis, paranoid reaction. *Rare:* Ataxia.

Respiratory System: *Frequent:* Cough increased, bronchitis. *Infrequent:* Dyspnea, asthma, pneumonia, laryngismus. *Rare:* Epistaxis, laryngitis, yawn.

Skin and Appendages: *Frequent:* Pruritus, sweating, acne. *Infrequent:* Dry skin, maculopapular rash, contact dermatitis, urticaria, herpes simplex, alopecia, vesiculobullous rash, herpes zoster, skin hypertrophy, fungal dermatitis, skin benign neoplasm. *Rare:* Eczema.

Special Senses: *Frequent:* Taste perversion, tinnitus. *Infrequent:* Dry eyes, conjunctivitis, ear pain, eye pain, otitis media, parosmia. *Rare:* Mydriasis, otitis external, visual field defect.

Urogenital System: *Frequent:* Urinary tract infection, urinary frequency, dysmenorrhea, metrorrhagia. *Infrequent:* Urinary tract infection (male), vaginitis, cystitis (female), hematuria (female), unintended pregnancy, dysuria (female), urinary urgency (male and female), vaginal moniliasis, menorrhagia, urination impaired (male), breast neoplasm (female), kidney calculus (female), vaginal hemorrhage, amenorrhea, breast pain, polyuria (female).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

EMSAM (selegiline transdermal system) is not a controlled substance.

Physical and Psychological Dependence

Several animal studies have assessed potential for abuse and/or dependence with chronic selegiline administration. None of these studies demonstrated a potential for selegiline abuse or dependence.

EMSAM 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, these observations were not systematic and 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. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of **EMSAM** misuse or abuse (e.g., development of tolerance, increases in dose, or drug-seeking behavior).

OVERDOSAGE

There are no specific antidotes for **EMSAM.** If symptoms of overdosage occur, immediately remove the **EMSAM** system and institute appropriate supportive therapy. For contemporary consultation on the management of poisoning or overdosage, contact the National Poison Control Center at 1-800-222-1222.

EMSAM is considered to be an irreversible MAOI at therapeutic doses and, in overdosage, is likely to cause excessive MAO-A inhibition, and may result in the signs and symptoms resembling overdosage with other non-selective, oral MAOI antidepressants (e.g., tranylcypromine [Parnate®], phenelzine [Nardil®], or isocarboxazide [Marplan®]).

Overdosage With Non-Selective MAO Inhibition

NOTE: The following is provided for reference only; it does not describe events that have actually been observed with selegiline in overdosage. No information regarding overdose by ingestion of **EMSAM** is available.

Typical signs and symptoms associated with overdosage of non-selective MAOI antidepressants may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur, and peak effects may not be observed for 24-48 hours. Since death has been reported following overdosage with MAOI agents, hospitalization with close monitoring during this period is essential.

Overdosage with MAOI agents is typically associated with CNS and cardiovascular toxicity. Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, convulsions, coma, rapid and irregular pulse, hypertension, hypotension and vascular collapse, precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin. Type and intensity of symptoms may be related to extent of the overdosage.

Treatment should include supportive measures, with pharmacological intervention as appropriate. Symptoms may persist after drug washout because of the irreversible inhibitory effects of these agents on systemic MAO activity. With overdosage, in order to avoid the occurrence of hypertensive crisis ("cheese reaction"), dietary tyramine should be restricted for several weeks beyond recovery to permit regeneration of the peripheral MAO-A isoenzyme.

DOSAGE AND ADMINISTRATION

Initial Treatment

EMSAM should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm once every 24 hours. The recommended starting dose and target dose for **EMSAM** is 6 mg/24 hours. **EMSAM** has been systematically evaluated and shown to be effective in a dose range of 6 mg/24 hours to 12 mg/24 hours. However, the trials were not designed to assess if higher doses are more effective than the lowest effective dose of 6 mg/24 hours. Based on clinical judgment, if dose increases are indicated for individual patients, they should occur in dose increments of 3 mg/24 hours (up to a maximum dose of 12 mg/24 hours) at intervals of no less than 2 weeks. As with all antidepressant drugs, full antidepressant effect may be delayed.

Patients should be informed that tyramine-rich foods and beverages should be avoided beginning on the first day of **EMSAM** 9 mg/24 hours or 12 mg/24 hours treatment and should continue to be avoided for 2 weeks after a dose reduction to **EMSAM** 6 mg/24 hours or following the discontinuation of **EMSAM** 9 mg/24 hours or 12 mg/24 hours (see **WARNINGS**).

Special Populations

No dosage adjustment is required for patients with mild to moderate renal or hepatic impairment. The recommended dose for elderly patients (≥65 years) is **EMSAM** 6 mg/24 hours daily. Dose increases, in the elderly, should be made with caution and patients should be closely observed for postural changes in blood pressure throughout treatment.

How to Use EMSAM

1. **EMSAM** should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm. A new application site should be selected with each new patch to avoid re-application to the same site on consecutive days. Patches should be applied at approximately the same time each day.
2. Apply the patch to an area of skin that is not hairy, oily, irritated, broken, scarred or calloused. Do not place the patch where your clothing is tight, which could cause the patch to rub off.
3. After you have selected the site for your patch, wash the area gently and thoroughly with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.
4. Just before you apply the patch, remove it from the pouch. Remove half of the protective backing and throw it away. Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers.
5. Press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface.
6. After you have applied the patch, wash your hands thoroughly with soap and water to remove any medicine that may have gotten on them. Do not touch your eyes until after you have washed your hands.
7. After 24 hours, remove the patch. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.
8. Throw away the folded patch so that children and/or pets cannot reach it.
9. Wash your hands with soap and water.
10. If your patch falls off, apply a new patch to a new site and resume your previous schedule.
11. Only one **EMSAM** patch should be worn at a time.
12. Avoid exposing the **EMSAM** application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Maintenance Treatment

It is generally agreed that episodes of depression require several months or longer of sustained pharmacologic therapy. The benefit of maintaining depressed patients on therapy with **EMSAM** at a dose of 6 mg/24 hours after achieving a responder status for an average duration of about 25 days was demonstrated in a controlled trial (see **Clinical Efficacy Trials** in Full Prescribing Information and **INDICATIONS AND USAGE**). The physician who elects to use **EMSAM** for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

DISTRIBUTED BY:

Bristol-Myers Squibb Company
Princeton, NJ 08543 U.S.A.

MANUFACTURED FOR:

Somerset PHARMACEUTICALS, INC.
Tampa, FL 33607 USA

April 2006
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EMSAM:PIR4

Depression can recur many times...

Or not.

Extending the body of evidence

2-YEAR RECURRENCE PREVENTION data for EFFEXOR XR[1]

IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents

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

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

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

Length and results of positive, randomized, double-blind, placebo-controlled antidepressant clinical studies[1]

CLINICAL DATA

	6 months	1 year	2 years
EFFEXOR XR® (venlafaxine HCl)	✔	✔	✔
Cymbalta® (duloxetine HCl)	✔		
Lexapro® (escitalopram oxalate)	✔	✔	
Wellbutrin XL® (bupropion HCl)	✔		
Zoloft® (sertraline HCl)	✔	✔	*
Paxil® (paroxetine HCl)	✔	✔	†

✔ = demonstrated relapse/recurrence prevention at end point.

***Zoloft has been studied in 2-year recurrence prevention as monotherapy but failed to show a significant difference vs. placebo at end point. Wilson KCM, et al. *Br J Psychiatry.* 2003;182:492-497.**

†Paxil has been studied in 2-year recurrence prevention in combination with psychotherapy/clinical management sessions with or without augmentation, but not as monotherapy. In patients with recurrent depression, no significant difference was seen between Paxil and placebo. Reynolds CF, et al. *N Engl J Med.* 2006;354:1130-1138.

In the EFFEXOR XR PREVENT study, patients had at least 3 prior episodes of depression in their lifetime.

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

Please see brief summary of Prescribing Information on adjacent pages.

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VENLAFAXINE HCl
EFFEXOR XR® EXTENDED RELEASE CAPSULES

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Dialogues

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

Dialogues

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

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

- The most common adverse events reported in EFFEXOR XR short-term placebo-controlled depression, 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.

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The change they deserve.

Reference: 1. Data on file, Wyeth Pharmaceuticals Inc.

Please see brief summary of Prescribing Information on adjacent pages.

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EFFEXOR XR® EXTENDED RELEASE CAPSULES

BRIEF SUMMARY. See package insert for full prescribing information.

Suicidality in Children and Adolescents

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

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

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

Effexor XR (8%) than placebo (4%) patients in MDD studies. The discontinuation rate for anorexia was 1.0% in MDD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (2%) patients in GAD studies. The discontinuation rate for anorexia was 0.9% for up to 8 weeks in GAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (20%) than placebo (2%) patients in SAD studies. The discontinuation rate for anorexia was 0.4% for up to 12 weeks in SAD studies. Treatment-emergent anorexia was more commonly reported for Effexor XR (8%) than placebo (3%) patients in PD studies. The discontinuation rate for anorexia was 0.4% for Effexor XR patients in 12-week PD studies. ***Pediatric Patients***: Decreased appetite was seen in pediatric patients receiving Effexor XR. In GAD and MDD trials, 10% of Effexor XR patients aged 6-17 for up to 8 weeks and 3% of placebo patients had treatment-emergent anorexia. None of the patients receiving Effexor XR discontinued for anorexia or weight loss. In the placebo-controlled trial for SAD, 22% and 3% of patients aged 8-17 treated for up to 16 weeks with Effexor XR and placebo, respectively, reported treatment-emergent anorexia (decreased appetite). The discontinuation rates for anorexia were 0.7% and 0.0% for patients receiving Effexor XR and placebo, respectively; the discontinuation rates for weight loss were 0.7% for patients receiving either Effexor XR or placebo. ***Activation of Mania/Hypomania***: Mania or hypomania has occurred during short-term depression and PD studies. As with all drugs effective in the treatment of MDD, Effexor XR should be used cautiously in patients with a history of mania. ***Hyponatremia***: Hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur with venlafaxine. Consider this in patients who are volume-depleted, elderly, or taking diuretics. ***Seizures***: In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine patients. Use cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures. ***Abnormal Bleeding***: Abnormal bleeding (most commonly ecchymosis) has been reported. ***Serum Cholesterol Elevation***: Clinically relevant increases in serum cholesterol were seen in 5.3% of venlafaxine patients and 0.0% of placebo patients treated for at least 3 months in trials. Consider measurement of serum cholesterol levels during long-term treatment. ***Use in Patients With Concomitant Illness***: Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. Increases in QT interval (QTc) have been reported in clinical studies. Exercise caution in patients whose underlying medical conditions might be compromised by increases in heart rate. In patients with renal impairment or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients. **Information for Patients**—Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Effexor XR and should counsel them in its appropriate use. A patient *Medication Guide About Using Antidepressants in Children and Teenagers* is available for Effexor XR. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is available at www.effexorxr.com or in the approved prescribing information. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking Effexor XR. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of symptoms listed in **WARNINGS: Clinical Worsening and Suicide Risk**, especially those seen early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to observe for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. Caution patients 1) about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities; 2) to avoid alcohol while taking Effexor XR; and 3) about the risk of serotonin syndrome with the concomitant use of Effexor XR and triptans, tramadol, tryptophan supplements, or other serotonergic agents. Patients should be advised to notify their physician 1) if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) about other prescription or over-the-counter drugs, including herbal preparations and nutritional supplements they are taking or plan to take; 3) if they develop a rash, hives, or related allergic phenomena; or 4) if they have a history of glaucoma or increased intraocular pressure. **Laboratory Tests**—No specific laboratory tests are recommended. **Drug Interactions**—***Alcohol***: A single dose of ethanol had no effect on the pharmacokinetics (PK) of venlafaxine or O-desmethylvenlafaxine (ODV), and venlafaxine did not exaggerate the psychomotor and psychometric effects induced by ethanol. ***Cimetidine***: Use caution when administering venlafaxine with cimetidine to patients with pre-existing hypertension or hepatic dysfunction, and the elderly. ***Diazepam***: A single dose of diazepam did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine did not have any effect on the PK of diazepam or its active metabolite, desmethyldiazepam, or affect the psychomotor and psychometric effects induced by diazepam. ***Haloperidol***: Venlafaxine decreased total oral-dose clearance of haloperidol, resulting in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88%, but the haloperidol elimination half-life was unchanged. ***Lithium***: A single dose of lithium did not appear to affect the PK of either venlafaxine or ODV. Venlafaxine had no effect on the PK of lithium. ***Drugs Highly Bound to Plasma Proteins***: Venlafaxine is not highly bound to plasma proteins; coadministration of Effexor XR with a highly protein-bound drug should not cause increased free concentrations of the other drug. ***Drugs That Inhibit Cytochrome P450 Isoenzymes***: CYP2D6 Inhibitors: Venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor. Concomitant use of venlafaxine with drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Use caution if therapy includes venlafaxine and any agent(s) that produces simultaneous inhibition of these two enzyme systems. ***Drugs Metabolized by Cytochrome P450 Isoenzymes***: Venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4, CYP2C9 (in vitro), or CYP2C19. ***Imipramine***: Venlafaxine did not affect the PK of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by ~35% in the presence of venlafaxine. The 2-OH-desipramine AUCs increased by 2.5-4.5 fold. Imipramine did not affect the PK of venlafaxine and ODV. ***Risperidone***: Venlafaxine slightly inhibited the CYP2D6-mediated metabolism of risperidone to its active metabolite, 9-hydroxyrisperidone, resulting in a ~32% increase in risperidone AUC. Venlafaxine coadministration did not significantly alter the PK profile of the total active moiety (risperidone plus 9-hydroxyrisperidone). **CYP3A4**: Venlafaxine did not inhibit CYP3A4 in vitro and in vivo. ***Indinavir***: In a study of 9 healthy volunteers, venlafaxine administration resulted in a 28% decrease in the AUC of a single dose of indinavir and a 36% decrease in indinavir C_{max}. Indinavir did not affect the PK of venlafaxine and ODV. **CYP1A2**: Venlafaxine did not inhibit CYP1A2 in vitro and in vivo. **CYP2C9**: Venlafaxine did not inhibit CYP2C9 in vitro. In vivo, venlafaxine 75 mg by mouth every 12 hours did not alter the PK of a single 550-mg dose of tolbutamide or the CYP2C9-mediated formation of 4-hydroxy-tolbutamide. **CYP2C19**: Venlafaxine did not inhibit the metabolism of diazepam, which is partially metabolized by CYP2C19 (see *Diazepam* above). ***MAOIs***: See **CONTRAINDICATIONS** and **WARNINGS**. ***CNS-Active Drugs***: Use caution with concomitant use of venlafaxine and other CNS-active drugs. **Serotonergic Drugs and Triptans (see WARNINGS: Serotonin Syndrome):** Based on the mechanism of action of Effexor XR and the potential for serotonin syndrome, caution is advised when Effexor XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's wort. If concomitant treatment of Effexor XR with these drugs is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Effexor XR with tryptophan supplements is not recommended. ***Electroconvulsive Therapy (ECT)***: There are no clinical data establishing the benefit of ECT combined with Effexor XR treatment. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—***Carcinogenesis***: There was no increase in tumors in mice and rats given up to 1.7 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. ***Mutagenesis***: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the CHO/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the in vivo chromosomal aberration assay in rat bone marrow. ***Impairment of Fertility***: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m^2 basis. **Pregnancy**—***Teratogenic Effects***—***Pregnancy Category C***: Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m^2 basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed. ***Nonteratogenic Effects***: Neonates exposed to Effexor XR late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Complications can arise immediately upon delivery. Reports include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. This is consistent with a direct toxic effect of SNRIs or a drug discontinuation syndrome. In some cases, it is consistent with serotonin syndrome. When treating a pregnant woman with Effexor XR during the third trimester, carefully consider the potential risks and benefits of treatment and consider tapering Effexor XR in the third trimester. **Labor, Delivery, Nursing**—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use**—Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING** and **WARNINGS: Clinical Worsening and Suicide Risk**). No studies have adequately assessed the impact of Effexor XR on growth, development, and maturation of children and adolescents. Studies suggest Effexor XR may adversely affect weight and height (see **PRECAUTIONS-General**, *Changes in Height* and *Changes in Weight*). Should the decision be made to treat a pediatric patient with Effexor XR, regular monitoring of weight and height is recommended during treatment, particularly if long term. The safety of Effexor XR for pediatric patients has not been assessed for chronic treatment >6 months. In studies in patients aged 6-17, blood pressure and cholesterol increases considered to be clinically relevant were similar to that observed in adult patients. The precautions for adults apply to pediatric patients. **Geriatric Use**—No overall differences in effectiveness or safety were observed between geriatric and younger patients. Greater sensitivity of some older individuals cannot be ruled out. Hyponatremia and SIADH have been reported, usually in the elderly. **ADVERSE REACTIONS**: ***Associated with Discontinuation of Treatment***—The most common events leading to discontinuation in MDD, GAD, SAD, and PD trials included nausea, anorexia, anxiety, impotence, dry mouth, dizziness, insomnia, somnolence, hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, abnormal (mostly delayed) ejaculation, asthenia, vomiting, nervousness, headache, vasodilatation, thinking abnormal, decreased libido, and sweating. ***Commonly Observed Adverse Events in Controlled Clinical Trials for MDD, GAD, SAD, and PD***—Body as a Whole: asthenia, headache, flu syndrome, accidental injury, abdominal pain. Cardiovascular: vasodilatation, hypertension, palpitation. Digestive: nausea, constipation, anorexia, vomiting, flatulence, diarrhea, eructation. Metabolic/Nutritional: weight loss. Nervous System: dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, hypertonia, paresthesia, libido decreased, agitation, anxiety, twitching. Respiratory System: pharyngitis, yawn, sinusitis. Skin: sweating. Special Senses: abnormal vision. Urogenital System: abnormal ejaculation, impotence, orgasmic dysfunction (including anorgasmia) in females. ***Vital Sign Changes***: Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min in depression and GAD trials and a mean increase in pulse rate of 4 beats/min in SAD trials. (See **WARNINGS-Sustained Hypertension**). ***Laboratory Changes***: Clinically relevant increases in serum cholesterol were noted in Effexor XR clinical trials. Increases were duration dependent over the study period and tended to be greater with higher doses. ***Other Events Observed During the Premarketing Evaluation of Effexor and Effexor XR***—N=6,670. "Frequent"=events occurring in at least 1/100 patients; "infrequent"=1/100 to 1/1000 patients; "rare"=fewer than 1/1000 patients. **Body as a whole** - Frequent: chest pain substernal, chills, fever, neck pain; Infrequent: face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt, withdrawal syndrome; Rare: appendicitis, bacteremia, carcinoma, cellulitis. **Cardiovascular system** - Frequent: migraine, postural hypotension, tachycardia; Infrequent: angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; Rare: aortic aneurysm, arteritis, first-degree atrioventricular block, bigeminy, bundle branch block, capillary fragility, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, hematoma, cardiovascular disorder (mitral valve and circulatory disturbance), mucocutaneous hemorrhage, myocardial infarct, pallor, sinus arrhythmia. **Digestive system** - Frequent: increased appetite; Infrequent: bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal hemorrhage, hemorrhoids, melena, oral moniliasis, stomatitis, mouth ulceration; Rare: abdominal distension, biliary pain, cheilitis, cholecystitis, cholelithiasis, esophageal spasms, duodenitis, hematemesis, gastroesophageal reflux disease, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, liver tenderness, parotitis, periodontitis, proctitis, rectal disorder, salivary gland enlargement, increased salivation, soft stools, tongue discoloration. **Endocrine system** - Rare: galactorrhoea, goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. **Hemic and lymphatic system** - Frequent: ecchymosis; Infrequent: anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia; Rare: basophilia, bleeding time increased, cyanosis, eosinophilia, lymphocytosis, multiple myeloma, purpura, thrombocytopenia. **Metabolic and nutritional** - Frequent: edema, weight gain; Infrequent: alkaline phosphatase increased, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hypoglycemia, hypokalemia, SGOT increased, SGPT increased, thirst; Rare: alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, glycosuria, gout, healing abnormal, hemochromatosis, hypercalcinuria, hyperkalemia, hyperphosphatemia, hyperuricemia, hypocholesteremia, hyponatremia, hypophosphatemia, hypoproteinemia, uremia. **Musculoskeletal system** - Frequent: arthralgia; Infrequent: arthritis, arthrosis, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; Rare: bone pain, pathological fracture, muscle cramp, muscle spasms, musculoskeletal stiffness, myopathy, osteoporosis, osteosclerosis, plantar fasciitis, rheumatoid arthritis, tendon rupture. **Nervous system** - Frequent: amnesia, confusion, depersonalization, hypesthesia, thinking abnormal, trismus, vertigo; Infrequent: akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; Rare: abnormal/changed behavior, adjustment disorder, akinesia, alcohol abuse, aphasia, bradykinesia, buccoglossal syndrome, cerebrovascular accident, feeling drunk, loss of consciousness, delusions, dementia, dystonia, energy increased, facial paralysis, abnormal gait, Guillain-Barré syndrome, homicidal ideation, hyperchlorhydria, hypokinesia, hysteria, impulse control difficulties, libido increased, motion sickness, neuritis, nystagmus, paranoid reaction, paresis, psychotic depression, reflexes decreased, reflexes increased, torticollis. **Respiratory system** - Frequent: cough increased, dyspnea; Infrequent: asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; Rare: atelectasis, hemoptysis, hypoventilation, hypoxia, larynx edema, pleurisy, pulmonary embolus, sleep apnea. **Skin and appendages** - Frequent: pruritus; Infrequent: acne, alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, psoriasis, urticaria; Rare: brittle nails, erythema nodosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, miliaria, petechial rash, pruritic rash, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin hypertrophy, skin striae, sweating decreased. **Special senses** - Frequent: abnormality of accommodation, mydriasis, taste perversion; Infrequent: conjunctivitis, diplopia, dry eyes, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; Rare: blepharitis, cataract, chromatopsia, conjunctival edema, corneal lesion, deafness, exophthalmos, eye hemorrhage, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. **Urogenital system** - Frequent: prostatic disorder (prostatitis, enlarged prostate, and prostate irritability), urination impaired; Infrequent: albuminuria, amenorrhea, cystitis, dysuria, hematuria, kidney calculus, kidney pain, leukorrhea, menorrhagia, metrorrhagia, nocturia, breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage, vaginitis; Rare: abortion, anuria, balanitis, bladder pain, breast discharge, breast engorgement, breast enlargement, endometriosis, female lactation, fibrocystic breast, calcium crystalluria, cervicitis, orchitis, ovarian cyst, prolonged erection, gynecomastia (male), hypomenorrhea, kidney function abnormal, mastitis, menopause, pyelonephritis, oliguria, salpingitis, urolithiasis, uterine hemorrhage, uterine spasm, vaginal dryness. **Postmarketing Reports**: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities such as QT prolongation; cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, and rare reports of ventricular fibrillation and ventricular tachycardia, including torsades de pointes; epidermal necrosis/Stevens-Johnson syndrome, erythema multiforme, extrapyramidal symptoms (including dyskinesia and tardive dyskinesia), angle-closure glaucoma, hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), interstitial lung disease (including pulmonary eosinophilia), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), neutropenia, night sweats, pancreatitis, pancytopenia, panic, prolactin increased, renal failure, rhabdomyolysis, serotonin syndrome, shock-like electrical sensations or tinnitus (in some cases, subsequent to the discontinuation of venlafaxine or tapering of dose), and SIADH (usually in the elderly). Elevated clozapine levels that were temporally associated with adverse events, including seizures, have been reported following the addition of venlafaxine. Increases in prothrombin time, partial thromboplastin time, or INR have been reported when venlafaxine was given to patients on warfarin therapy. **DRUG ABUSE AND DEPENDENCE**: Effexor XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of misuse or abuse. **OVERDOSAGE**: Electrocardiogram changes (e.g., prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, altered level of consciousness (ranging from somnolence to coma), rhabdomyolysis, seizures, vertigo, liver necrosis, and death have been reported. 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 W10404C024, revised June 2006.

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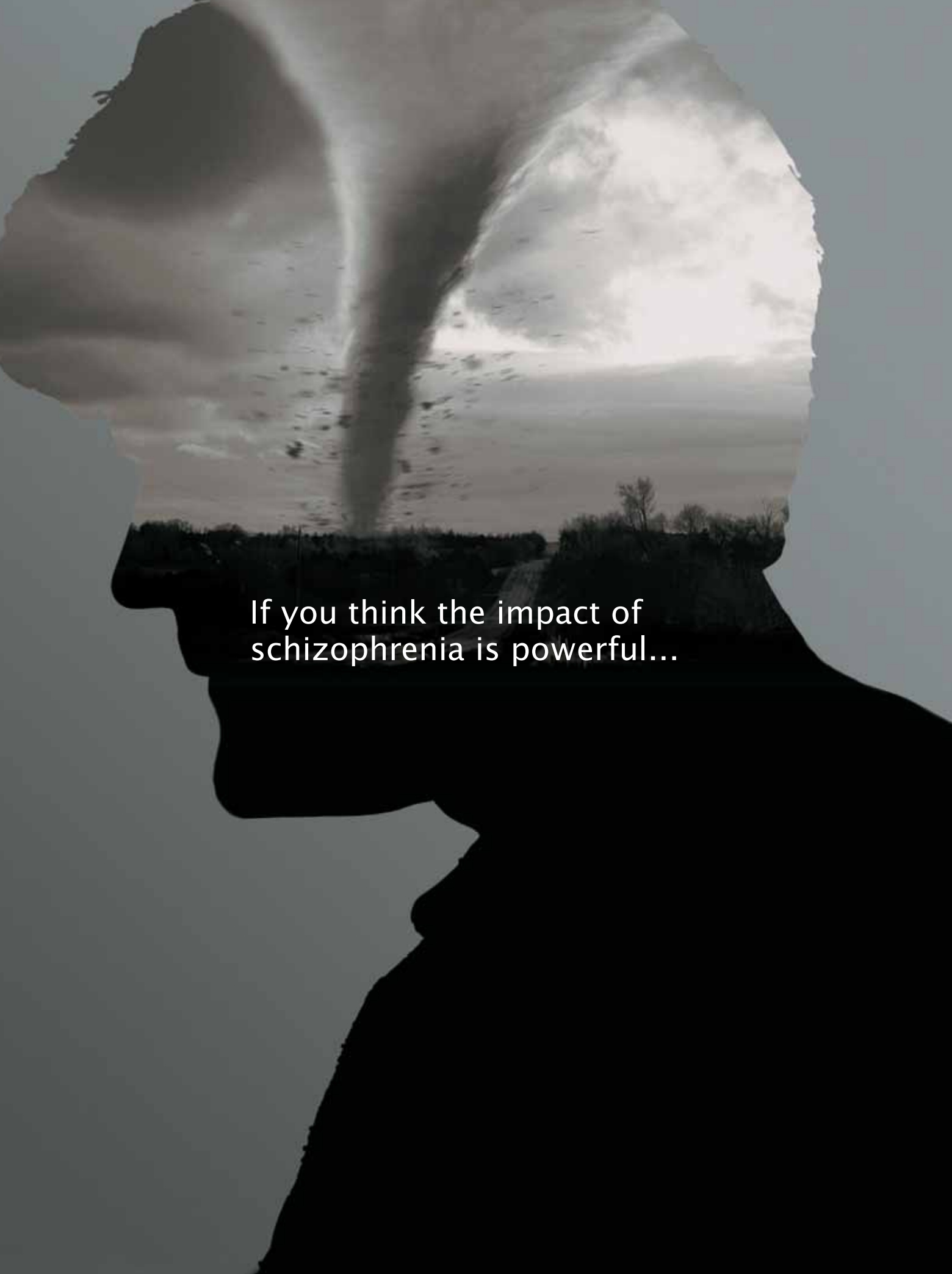
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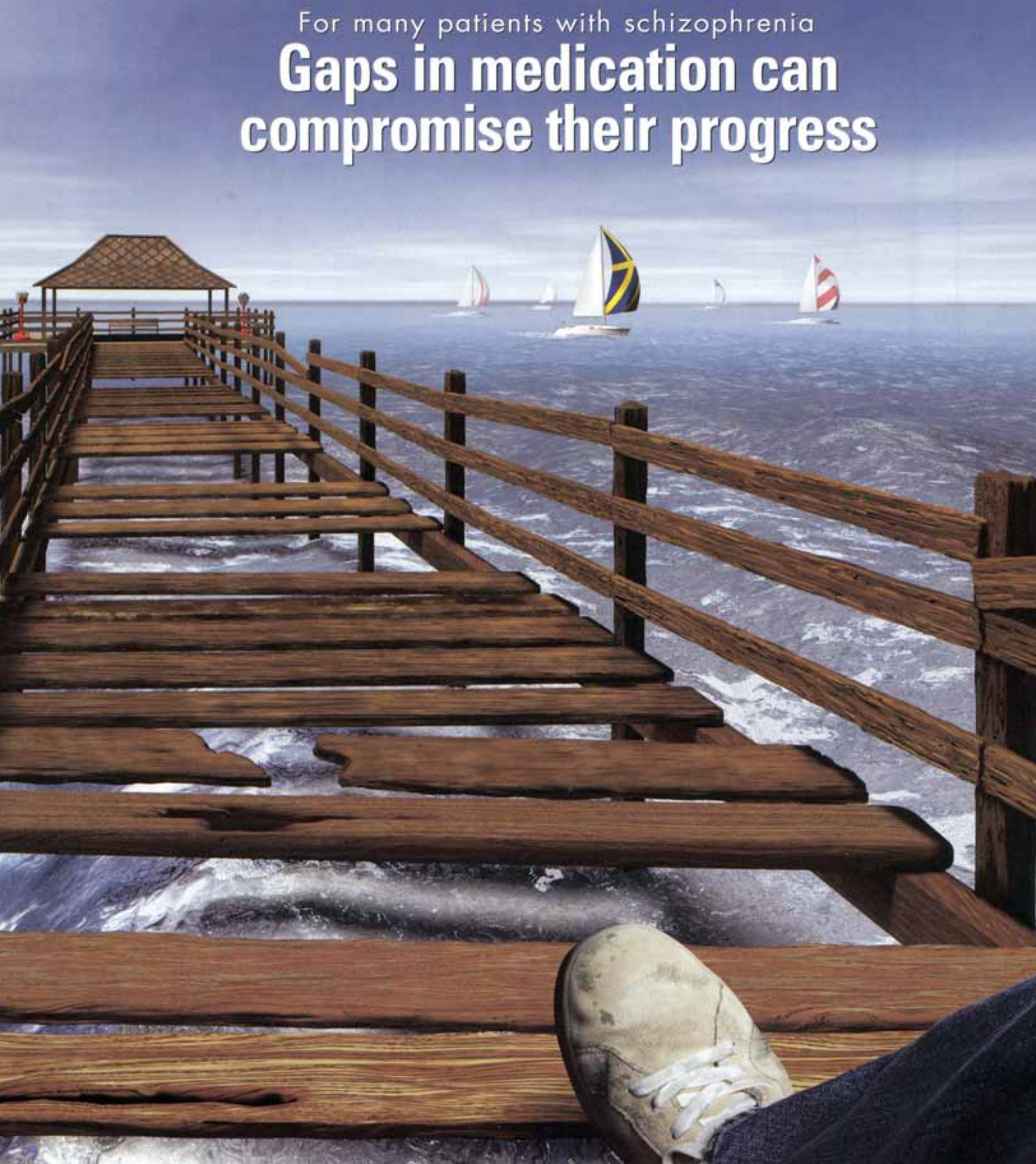

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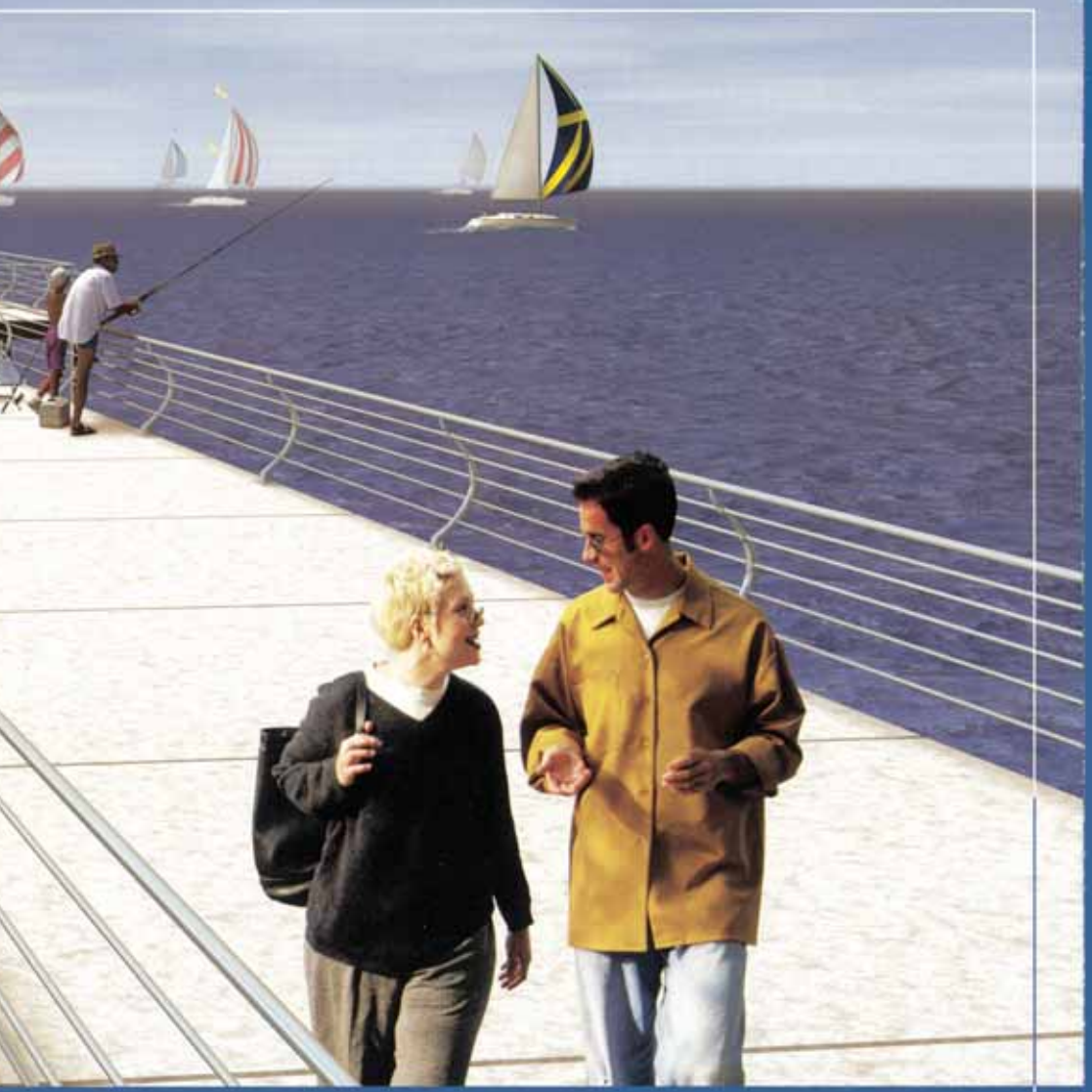
RISPERDAL CONSTA is indicated for the treatment of schizophrenia.

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® CONSTA® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

Commonly observed events: Treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL CONSTA groups (25 mg or 50 mg) and at least twice that of placebo were: somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue and weight increase.

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), including RISPERDAL CONSTA. 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.

Tardive dyskinesia (TD): As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD; if its signs and symptoms appear, discontinuation of RISPERDAL CONSTA should be considered. In the integrated database of multiple-dose studies the incidence of TD was 0.6% (9/1499 patients).



The only
long-acting atypical
antipsychotic

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risperidone Long-Acting Injection

Neuroleptic malignant syndrome (NMS): NMS has been reported rarely with this class of medications, including RISPERDAL CONSTA and appropriate management should be employed.

Cerebrovascular adverse events (CAEs): CAEs, including fatalities, have been reported in elderly patients with dementia-related psychosis taking oral risperidone in clinical trials. The incidence of CAEs with oral risperidone was significantly higher than with placebo. RISPERDAL CONSTA is not approved for treating these patients.

Please see brief summary of full Prescribing Information, including Boxed Warning, on adjacent page.

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Risperdal CONSTA
risperidone Long-Acting Injection

 August 2006 01CS560

Janssen L.P.

Risperdal CONSTA®

risperidone Long-Acting Injection

BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION OF WHICH THE FOLLOWING IS A BRIEF SUMMAh i.

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® CONSTA® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

INDICATIONS AND USAGE: RISPERDAL® CONSTA® (risperidone) is indicated for the treatment of schizophrenia.

CONTRAINDICATIONS: RISPERDAL® CONSTA® (risperidone) is contraindicated in patients with a known hypersensitivity to the product or any of its components.

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® CONSTA® (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 in association with antipsychotic drugs. 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:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. If signs and symptoms of tardive dyskinesia appear in a patient treated with RISPERDAL® CONSTA®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® CONSTA® despite the presence of the syndrome. **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 oral 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 oral risperidone compared to patients treated with placebo. RISPERDAL® CONSTA® 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 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® CONSTA® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.8% (12/1499 patients) of patients treated with RISPERDAL® CONSTA® in multiple-dose studies. Patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). RISPERDAL® CONSTA® should be used with particular caution in (1) 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, and (2) in the elderly and patients with renal or hepatic impairment. Monitoring of orthostatic vital signs should be considered in all such patients, and a dose reduction should be considered if hypotension occurs. Clinically significant hypotension has been observed with concomitant use of oral RISPERDAL® and antihypertensive medication. **Seizures:** During premarketing testing, seizures occurred in 0.3% (5/1499 patients) of patients treated with RISPERDAL® CONSTA®. Therefore, RISPERDAL® CONSTA® 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® CONSTA® 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.**) **Osteodystrophy and Tumors in Animals:** RISPERDAL® CONSTA® produced osteodystrophy in male and female rats in a 1-year toxicity study and a 2-year carcinogenicity study at a dose of 40 mg/kg administered IM every 2 weeks. RISPERDAL® CONSTA® produced renal tubular tumors (adenoma, adenocarcinoma) and adrenomedullary pheochromocytomas in male rats in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. In addition, RISPERDAL® CONSTA® produced an increase in a marker of cellular proliferation in renal tissue in males in the 1-year toxicity study and in renal tumor-bearing males in the 2-year carcinogenicity study at 40 mg/kg administered IM every 2 weeks. **Neither the renal or adrenal tumors, nor osteodystrophy, were seen in studies of orally administered risperidone.** Osteodystrophy was not observed in dogs at doses up to 14 times (based on AUC) the IM MRHD in a 1-year toxicity study. The renal tubular and adrenomedullary tumors in male rats and other tumor findings are described in more detail under PRECAUTIONS, Carcinogenicity, Mutagenesis, Impairment of Fertility. The relevance of these findings to human risk is unknown. **Hyperprolactinemia:** As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. 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 reported by 5% of patients treated with RISPERDAL® CONSTA® in multiple-dose trials. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that treatment with RISPERDAL® CONSTA® does not affect them adversely. **Priapism:** No cases of priapism have been reported in patients treated with RISPERDAL® CONSTA®. However, rare cases of priapism have been reported in patients treated with oral RISPERDAL®. **Thrombotic Thrombocytopenic Purpura (TTP):** A single case of TTP was reported in a 28 year-old female patient receiving oral 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. **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high-risk patients should accompany drug therapy. **Use in Patients with Concomitant Illness:** Clinical experience with RISPERDAL® CONSTA® in patients with certain concomitant systemic illnesses is limited. Patients with Parkinson's Disease or Dementia with Lewy Bodies who receive antipsychotics, including RISPERDAL® CONSTA®, may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medications. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms. Caution is advisable when using RISPERDAL® CONSTA® 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. Patients with renal or hepatic impairment should be carefully titrated on oral RISPERDAL® before treatment with RISPERDAL® CONSTA® is initiated (see DOSAGE AND ADMINISTRATION in full PI). **Drug Interactions:** The interactions of RISPERDAL® CONSTA® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® CONSTA® is administered in combination with other centrally-acting drugs or alcohol. Because of its potential for inducing hypotension, RISPERDAL® CONSTA® may enhance the hypotensive effects of other therapeutic agents with this potential. RISPERDAL® CONSTA® may antagonize the effects of levodopa and dopamine agonists. Amitriptyline did not affect the pharmacokinetics of risperidone or the active moiety. Cimetidine and ranitidine increased the bioavailability of risperidone by 64% and 26%, respectively. However, cimetidine did not affect the AUC of the active moiety, whereas ranitidine increased the AUC of the active moiety by 20%. 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 oral 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. 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. At the initiation of therapy with carbamazepine or other known hepatic enzyme inducers, patients should be closely monitored during the first 4-8 weeks, since the dose of RISPERDAL® CONSTA® may need to be adjusted. A dose increase, or additional oral RISPERDAL®, may need to be considered. On discontinuation of carbamazepine or other hepatic enzyme inducers, the dosage of RISPERDAL® CONSTA® should be re-evaluated and, if necessary, decreased. Patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentrations of risperidone plus 9–hydroxyrisperidone. For patients treated with the lowest available dose (25 mg) of RISPERDAL® CONSTA®, it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with RISPERDAL® CONSTA®. **Fluoxetine and Paroxetine:** Fluoxetine (20 mg QD) and paroxetine (20 mg QD), which inhibits CYP 2D6, 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 dosage of RISPERDAL® CONSTA®. When initiation of fluoxetine or paroxetine is considered, patients may be placed on a lower dose of RISPERDAL® CONSTA® between 2 to 4 weeks before the planned start of fluoxetine or paroxetine therapy to adjust for the expected increase in plasma concentrations of risperidone. For patients treated with the lowest available dose (25 mg), it is recommended to continue treatment with the 25-mg dose unless clinical judgment necessitates interruption of treatment with RISPERDAL® CONSTA®. 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 patients) 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® CONSTA® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. In drug interaction studies, oral risperidone did not significantly affect the pharmacokinetics of donepezil and galantamine, which are metabolized by CYP 2D6. **Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis - Oral:** 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 oral maximum recommended human dose (MRHD) (16 mg/day) on a mg/kg basis, or 0.2, 0.75, and 3 times the oral MRHD (mice) or 0.4, 1.5, and 6 times the oral MRHD (rats) on a mg/m^2 basis. A maximum tolerated dose was not achieved in male mice. There was a significant increase in pituitary gland adenomas in female mice at doses 0.75 and 3 times the oral MRHD on a mg/m^2 basis. There was a significant increase in endocrine pancreatic adenomas in male rats at doses 1.5 and 6 times the oral MRHD on a mg/m^2 basis. Mammary gland adenocarcinomas were significantly increased in female mice at all doses tested (0.2, 0.75, and 3 times the oral MRHD on a mg/m^2 basis), in female rats at all doses tested (0.4, 1.5, and 6 times the oral MRHD on a mg/m^2 basis), and in male rats at a dose 6 times the oral MRHD on a mg/m^2 basis. **Carcinogenesis - IM:** RISPERDAL® CONSTA® was evaluated in a 24-month carcinogenicity study in which SPF Wistar rats were treated every 2 weeks with IM injections of either 5 mg/kg or 40 mg/kg of risperidone. These doses are 1 and 8 times the MRHD (50 mg) on a mg/m^2 basis. A control group received injections of 0.9% NaCl, and a vehicle control group was injected with placebo microspheres. There was a significant increase in pituitary gland adenomas, endocrine pancreas adenomas, and adrenomedullary pheochromocytomas at 8 times the IM MRHD on a mg/m^2 basis. The incidence of mammary gland adenocarcinomas was significantly increased in female rats at both doses (1 and 8 times the IM MRHD on a mg/m^2 basis). A significant increase in renal tubular tumors (adenoma, adenocarcinomas) was observed in male rats at 8 times the IM MRHD on a mg/m^2 basis. Plasma exposures (AUC) in rats were 0.3 and 2 times (at 5 and 40 mg/kg, respectively) the expected plasma exposure (AUC) at the IM MRHD. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see PRECAUTIONS - Hyperprolactinemia). **Mutagenesis:** No evidence of mutagenic potential for oral risperidone was found. In addition, no evidence of mutagenic potential was found in the *in vitro* Ames reverse mutation test for RISPERDAL® CONSTA®. **Impairment of Fertility:** Oral 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 oral maximum recommended human dose. No mating and fertility studies were conducted with RISPERDAL® CONSTA®. **Pregnancy: Pregnancy Category C:** The teratogenic potential of oral risperidone was studied in three embryofetal development studies in Sprague-Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the oral maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one embryofetal development study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the oral 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 oral MRHD on a mg/m^2 basis. In three reproductive studies in rats (two peri/postnatal development studies 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 oral 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 peri/post-natal development study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the oral 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 Days 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 oral MRHD on a mg/m^2 basis. No studies were conducted with RISPERDAL® CONSTA®. 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 oral RISPERDAL® therapy is unknown. Reversible extrapyramidal symptoms in the neonate were observed following postmarketing use of risperidone during the last trimester of pregnancy. RISPERDAL® CONSTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of RISPERDAL® CONSTA® 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 should not breast-feed during treatment with RISPERDAL® CONSTA® and for at least 12 weeks after the last injection. **Pediatric Use:** RISPERDAL® CONSTA® has not been studied in children younger than 18 years old. **Geriatric Use:** In an open-label study, 57 clinically stable, elderly patients (≥65 years old) with schizophrenia or schizoaffective disorder received RISPERDAL® CONSTA® every 2 weeks for up to 12 months. In general, no differences in the tolerability of RISPERDAL® CONSTA® were observed between otherwise healthy elderly and nonelderly patients. Therefore, dosing recommendations for otherwise healthy elderly patients are the same as for nonelderly patients. Because elderly patients exhibit a greater tendency to orthostatic hypotension than nonelderly patients, elderly patients should be instructed in nonpharmacologic interventions that help to reduce the occurrence of orthostatic hypotension (e.g., sitting on the edge of the bed for several minutes before attempting to stand in the morning and slowly rising from a seated position). In addition, monitoring of orthostatic vital signs should be considered in elderly patients for whom orthostatic hypotension is of concern (see PRECAUTIONS, DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY 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 oral risperidone when compared to patients treated with oral risperidone alone or with oral 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 oral risperidone regardless of concomitant use with furosemide. RISPERDAL® CONSTA® 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: In the 12-week, placebo-controlled trial, the incidence of schizophrenic patients who discontinued treatment due to an adverse event was lower with RISPERDAL® CONSTA® (11%, 22/202 patients) than with placebo (13%; 13/98 patients). **Incidence in Controlled Trials: Commonly Observed Adverse Events in Controlled Clinical Trials:** Spontaneously reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® CONSTA® groups (25 mg or 50 mg) and at least twice that of placebo were: somnolence, akathisia, parkinsonism, dyspepsia, constipation, dry mouth, fatigue, weight increase. **Dose Dependency of Adverse Events:** ***Extrapyramidal Symptoms:*** The overall incidence of EPS-related adverse events (akathisia, dystonia, parkinsonism, and tremor) in patients treated with 25 mg RISPERDAL® CONSTA® was comparable to that of patients treated with placebo; the incidence of EPS-related adverse events was higher in patients treated with 50 mg RISPERDAL® CONSTA®. **Vital Sign Changes:** RISPERDAL® is associated with orthostatic hypotension and tachycardia (see PRECAUTIONS). In the placebo-controlled trial, orthostatic hypotension was observed in 2% of patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® (see PRECAUTIONS). **Weight Changes:** In the 12-week, placebo-controlled trial, 9% of patients treated with RISPERDAL® CONSTA®, compared with 6% of patients treated with placebo, experienced a weight gain of >7% of body weight at endpoint. **Laboratory Changes:** The percentage of patients treated with RISPERDAL® CONSTA® who experienced potentially important changes in routine serum chemistry, hematology, or urinalysis parameters was similar to or less than that of placebo patients. Additionally, no patients discontinued treatment due to changes in serum chemistry, hematology, or urinalysis parameters. **ECG Changes:** The electrocardiograms of 202 schizophrenic patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® and 98 schizophrenic patients treated with placebo in a 12-week, double-blind, placebo-controlled trial were evaluated. Compared with placebo, there were no statistically significant differences in QTc intervals (using Fridericia's and linear correction factors) during treatment with RISPERDAL® CONSTA®. **Pain Assessment and Local Injection Site Reactions:** The mean intensity of injection pain reported by patients using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 16.7 to 12.6; 25 mg: 12.0 to 9.0; 50 mg: 18.2 to 11.8). After the sixth injection (Week 10), investigator ratings indicated that 1% of patients treated with 25 mg or 50 mg RISPERDAL® CONSTA® experienced redness, swelling, or induration at the injection site. **Other Events Observed During the Premarketing Evaluation of RISPERDAL® CONSTA®:** During its premarketing assessment, RISPERDAL® CONSTA® was administered to 1499 patients in multiple-dose studies. The conditions and duration of exposure to RISPERDAL® CONSTA® varied greatly, and included (in overlapping categories) open-label and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies, and short-term and long-term exposure studies. 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; rare events are those occurring in fewer than 1/1000 patients. It is important to emphasize that, although the reported events occurred during treatment with RISPERDAL® CONSTA®, they were not necessarily caused by it.) **Psychiatric Disorders:** *Frequent:* anxiety, psychosis, depression, agitation, nervousness, paranoid reaction, delusion, apathy. *Infrequent:* anorexia, impaired concentration, impotence, emotional lability, manic reaction, decreased libido, increased appetite, amnesia, confusion, euphoria, depersonalization, paroniria, delirium, psychotic depression. **Central and Peripheral Nervous System Disorders:** *Frequent:* hypertonia, dystonia. *Infrequent:* dyskinesia, vertigo, leg cramps, tardive dyskinesia[a], involuntary muscle contractions, paraesthesia, abnormal gait, bradykinesia, convulsions, hypokinesia, ataxia, fecal incontinence, oculogyric crisis, tetany, apraxia, dementia, migraine. *Rare:* neuroleptic malignant syndrome. [a]In the integrated database of multiple-dose studies (1499 patients with schizophrenia or schizoaffective disorder), 9 patients (0.6%) treated with RISPERDAL® CONSTA® (all dosages combined) experienced an adverse event of tardive dyskinesia. **Body as a Whole/General Disorders:** *Frequent:* back pain, chest pain, asthenia. *Infrequent:* malaise, choking. **Gastrointestinal Disorders:** *Frequent:* nausea, vomiting, abdominal pain. *Infrequent:* gastritis, gastroesophageal reflux, flatulence, hemorrhoids, melena, dysphagia, rectal hemorrhage, stomatitis, colitis, gastric ulcer, gingivitis, irritable bowel syndrome, ulcerative stomatitis. **Respiratory System Disorders:** *Frequent:* dyspnea. *Infrequent:* pneumonia, stridor, hemoptysis. *Rare:* pulmonary edema. **Skin and Appendage Disorders:** *Frequent:* rash. *Infrequent:* eczema, pruritus, erythematous rash, dermatitis, alopecia, seborrhea, photosensitivity reaction, increased sweating. **Metabolic and Nutritional Disorders:** *Infrequent:* hyperuricemia, hyperglycemia, hyperlipemia, hypokalemia, glycosuria, hypercholesterolemia, obesity, dehydration, diabetes mellitus, hyponatremia. **Musculo-Skeletal System Disorders:** *Frequent:* arthralgia, skeletal pain. *Infrequent:* torticollis, arthrosis, muscle weakness, tendinitis, arthritis, arthropathy. **Heart Rate and Rhythm Disorders:** *Frequent:* tachycardia. *Infrequent:* bradycardia, AV block, palpitation, bundle branch block. *Rare:* T-wave inversion. **Cardiovascular Disorders:** *Frequent:* hypotension. *Infrequent:* postural hypotension. **Urinary System Disorders:** *Frequent:* urinary incontinence. *Infrequent:* hematuria, micturition frequency, renal pain, urinary retention. **Vision Disorders:** *Infrequent:* conjunctivitis, eye pain, abnormal accommodation. **Reproductive Disorders, Female:** *Frequent:* amenorrhea. *Infrequent:* nonpuerperal lactation, vaginitis, dysmenorrhea, breast pain, leukorrhea. **Resistance Mechanism Disorders:** *Infrequent:* abscess. **Liver and Biliary System Disorders:** *Frequent:* increased hepatic enzymes. *Infrequent:* hepatomegaly, increased SGPT. *Rare:* bilirubinemia, increased GGT, hepatitis, hepatocellular damage, jaundice, fatty liver, increased SGOT. **Reproductive Disorders, Male:** *Infrequent:* ejaculation failure. **Application Site Disorders:** *Frequent:* injection site pain. *Infrequent:* injection site reaction. **Hearing and Vestibular Disorders:** *Infrequent:* earache, deafness, hearing decreased. **Red Blood Cell Disorders:** *Frequent:* anemia. **White Cell and Resistance Disorders:** *Infrequent:* lymphadenopathy, leucopenia, cervical lymphadenopathy. *Rare:* granulocytopenia, leukocytosis, lymphopenia. **Endocrine Disorders:** *Infrequent:* hyperprolactinemia, gynecomastia, hypothyroidism. **Platelet, Bleeding and Clotting Disorders:** *Infrequent:* purpura, epistaxis. *Rare:* pulmonary embolism, hematoma, thrombocytopenia. **Myo-, Endo-, and Pericardial and Valve Disorders:** *Infrequent:* myocardial ischemia, angina pectoris, myocardial infarction. **Vascular (Extracardiac) Disorders:** *Infrequent:* phlebitis. *Rare:* intermittent claudication, flushing, thrombophlebitis. **Postintroduction Reports:** Adverse events reported since market introduction which were temporally (but not necessarily causally) related to oral RISPERDAL® therapy include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, benign pituitary adenomas, cerebrovascular disorder, including cerebrovascular accident, diabetes mellitus aggravated, including diabetic ketoacidosis, hyperglycemia, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving oral RISPERDAL®. A causal relationship with oral 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® CONSTA® (risperidone) is not a controlled substance.

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

75195068 - US Patent 4,804,663 Revised November 2005 ©Janssen 2003

Janssen L.P.

01CS515BS

KNOW THE FACTS

41% of all patients had the metabolic syndrome at baseline in the landmark CATIE schizophrenia study.[1]

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

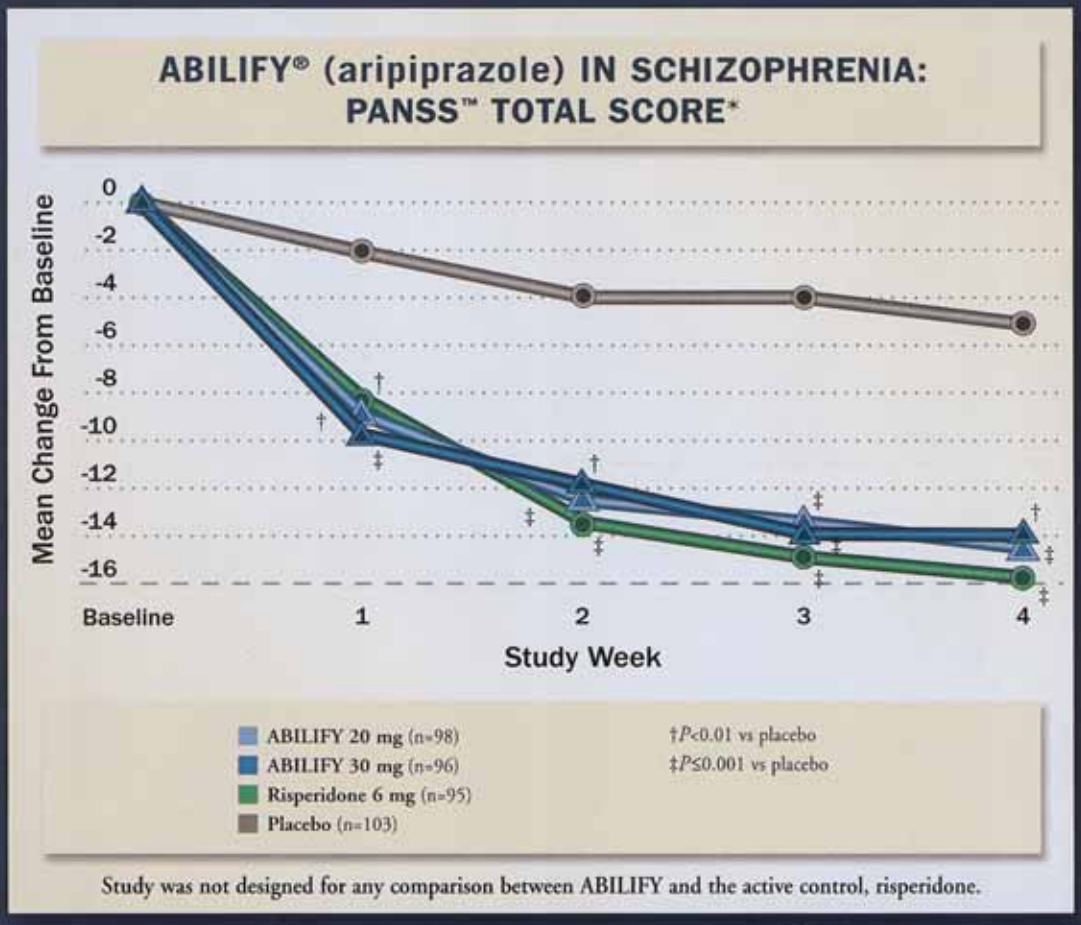
Pfizer

Reference: 1. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res.* 2005;80:19-32.

GZ274682

Printed in USA/May 2006

Controlling symptoms is one thing...



Data from a 4-week, double-blind, randomized, placebo-controlled trial (n=404) in hospitalized patients with acute **schizophrenia** or schizoaffective disorder. Mean baseline PANSS™ Total Scores: ABILIFY 20 mg 94.4, ABILIFY 30 mg 92.6, risperidone 6 mg 94.9, placebo 95.7. Mean change from baseline: ABILIFY 20 mg -14.5, ABILIFY 30 mg -13.9, risperidone 6 mg -15.7, placebo -5.0.

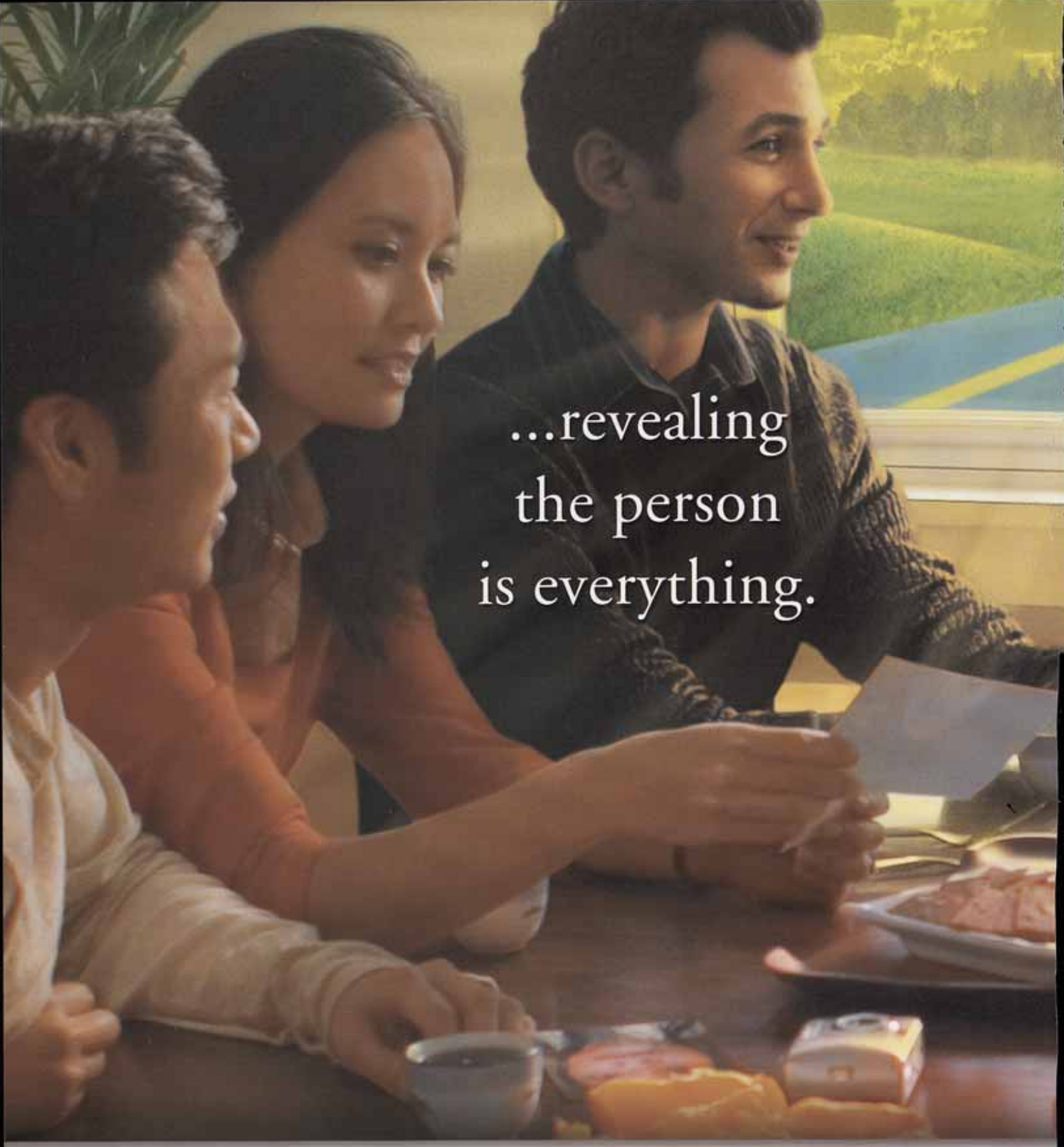
Potkin et al. *Arch Gen Psychiatry*. 2003.

*Last observation carried forward (LOCF).

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

ABILIFY is indicated for the treatment of schizophrenia.
A recommended starting and target dose of 10 or 15 mg/day is effective.

Please see IMPORTANT SAFETY INFORMATION, including **Bolded WARNING**, and INDICATIONS on page 4.



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. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular or infectious in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

Please see IMPORTANT SAFETY INFORMATION and INDICATIONS on page 4.

ABILIFY®
(aripiprazole)
TABLETS and ORAL SOLUTION 1 mg/mL

HELP ILLUMINATE THE PERSON WITHIN

IMPORTANT SAFETY INFORMATION and INDICATIONS for ABILIFY® (aripiprazole)

IMPORTANT SAFETY 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. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular or infectious in nature. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis (see Boxed WARNING).
- ABILIFY is contraindicated in patients with a known **hypersensitivity** to the product.
- As with all antipsychotic medications, including ABILIFY, a rare condition referred to as **neuroleptic malignant syndrome (NMS)** has been reported. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of **tardive dyskinesia (TD)**.
- **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, including a significant dose response relationship in a fixed-dose trial. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
- **Hyperglycemia**, including some serious cases ranging from ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics. Patients on ABILIFY should be appropriately tested before and monitored during treatment.

ABILIFY may be associated with **orthostatic hypotension** and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

As with other antipsychotic drugs, ABILIFY should be used with caution in patients with a history of **seizures** or with conditions that lower the seizure threshold.

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

Disruption of the body's ability to reduce **core body temperature** has been attributed to antipsychotics. Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

As antipsychotics have been associated with **esophageal dysmotility and aspiration**, ABILIFY should be used cautiously in patients at risk for aspiration pneumonia.

As the possibility of a **suicide** attempt is inherent in psychotic illness and bipolar disorder, close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY (aripiprazole) should be written for the smallest quantity consistent with good patient management to reduce the risk of overdose.

Physicians should determine if a patient is **pregnant** or intends to become pregnant while taking ABILIFY. Patients should be advised not to breast-feed while taking ABILIFY.

Patients should be advised to avoid alcohol while taking ABILIFY.

Both CYP3A4 and CYP2D6 are responsible for ABILIFY metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause an increase in ABILIFY clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit ABILIFY elimination and cause increased blood levels.

Commonly observed adverse events reported with ABILIFY in 3-week bipolar mania trials at a ≥5% incidence for ABILIFY and at a rate at least twice the rate of placebo include, respectively, akathisia (15% vs 4%), constipation (13% vs 6%), and accidental injury (6% vs 3%).

Treatment-emergent adverse events reported with ABILIFY in short-term trials at an incidence ≥10% and greater than placebo, respectively, include headache (31% vs 26%), agitation (25% vs 24%), anxiety (20% vs 17%), insomnia (20% vs 15%), nausea (16% vs 12%), dyspepsia (15% vs 13%), somnolence (12% vs 8%), akathisia (12% vs 5%), lightheadedness (11% vs 8%), vomiting (11% vs 6%), and constipation (11% vs 7%).

The adverse events reported in a 26-week, double-blind schizophrenia trial comparing ABILIFY and placebo were generally consistent with those reported in the short-term, placebo-controlled schizophrenia trials, except for a higher incidence of tremor: 9% for ABILIFY vs 1% for placebo.

INDICATIONS: ABILIFY is 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*
- Acute manic and mixed episodes associated with Bipolar I Disorder
- Maintaining efficacy in patients with Bipolar I Disorder with a recent manic or mixed episode who had been previously stabilized and then maintained for at least 6 weeks*

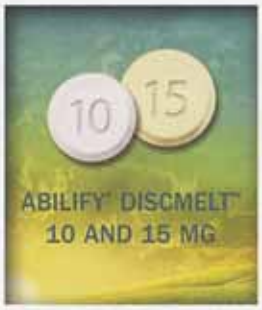
*Physicians who elect to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

ABILIFY is taken once daily with or without food.

Please see BRIEF SUMMARY of FULL PRESCRIBING INFORMATION, including **Boxed WARNING**, on the following pages.

New ABILIFY® DISCMELT™ (aripiprazole)

Orally Disintegrating Tablets



Similar efficacy and safety to ABILIFY tablets

No liquid needed

Rapidly disintegrates

Convenient delivery of an effective dose

ABILIFY® DISCMELT™ (aripiprazole)
ORALLY DISINTEGRATING TABLETS 15 mg

HELP ILLUMINATE THE PERSON WITHIN

ABILIFY®(aripiprazole) Tablets
ABILIFY® DISCMELT™ (aripiprazole)
Orally Disintegrating Tablets
ABILIFY®(aripiprazole) Oral Solution

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information please consult official package circular.

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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis.

CONTRAINDICATIONS

ABILIFY (aripiprazole) 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. ABILIFY is not approved for the treatment of patients with 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 in association with administration of antipsychotic drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole treatment in the premarketing worldwide clinical database. 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.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

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

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome 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 the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. 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. In patients who do 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 of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

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 (e.g., stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole 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**, and **PRECAUTIONS:** *Use in Patients with Concomitant Illness: Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease.*)

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. There have been few reports of hyperglycemia in patients treated with ABILIFY. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. 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. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include ABILIFY suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

Aripiprazole 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 ABILIFY (aripiprazole) included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on ABILIFY included: orthostatic hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%, aripiprazole 0.5%), and syncope (placebo 0.9%, aripiprazole 0.5%).

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 schizophrenia: 14% among aripiprazole-treated patients and 12% among placebo-treated patients and in bipolar mania: 3% among aripiprazole-treated patients and 2% among placebo-treated patients).

Aripiprazole 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).

Seizure

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients with schizophrenia in short-term, placebo-controlled trials. In short-term, placebo-controlled clinical trials of patients with bipolar mania, 0.3% (2/597) of aripiprazole-treated patients and 0.2% (1/436) of placebo-treated patients experienced seizures. As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that 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.

Potential for Cognitive and Motor Impairment

In short-term, placebo-controlled trials of schizophrenia, somnolence was reported in 11% of patients on ABILIFY compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% (1/926) of patients with schizophrenia on ABILIFY in short-term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar mania, somnolence was reported in 14% of patients on ABILIFY compared to 7% of patients on placebo, but did not lead to discontinuation of any patients with bipolar mania. 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. 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 the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

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. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **PRECAUTIONS:** *Use in Patients with Concomitant Illness*).

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 in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness

Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses (see **CLINICAL PHARMACOLOGY: Special Populations:** *Renal Impairment* and *Hepatic Impairment* in Full Prescribing Information) 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. Patients with these diagnoses were excluded from premarketing clinical studies.

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease: In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the treatment-emergent adverse events that were reported at an incidence of ≥3% and aripiprazole incidence at least twice that for placebo were asthenia (placebo 3%, aripiprazole 8%), somnolence (placebo 3%, aripiprazole 9%), urinary incontinence (placebo 1%, aripiprazole 5%), excessive salivation (placebo 0%, aripiprazole 4%), and lightheadedness (placebo 1%, aripiprazole 4%).

The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. 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 also **Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**, and **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis**.)

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY:

Interference with Cognitive and Motor Performance: Because aripiprazole may have 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 aripiprazole 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 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.

Alcohol: Patients should be advised to avoid alcohol while taking ABILIFY.

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

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

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.

Drug-Drug Interactions

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally acting drugs and alcohol. Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

Potential for Other Drugs to Affect ABILIFY

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (e.g., carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Ketoconazole: Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Quinidine: Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when concomitant administration of quinidine with aripiprazole occurs. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

Carbamazepine: Coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, aripiprazole dose should then be reduced.

No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions** in Full Prescribing Information).

Potential for ABILIFY (aripiprazole) to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 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. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions** in Full Prescribing Information).

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

Lifetime 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 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m^2). 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).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in 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 maximum recommended human dose [MRHD] on a 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 a 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

Pregnancy Category C

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg, however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of skeletal abnormality (fused sternebrae at 30 and 100 mg/kg) and minor skeletal variations (100 mg/kg).

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

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

Of the 7951 patients treated with aripiprazole in premarketing clinical trials, 991 (12%) were ≥65 years old and 789 (10%) were ≥75 years old. The majority (88%) of the 991 patients were diagnosed with dementia of the Alzheimer's type.

Placebo-controlled studies of 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 **Boxed WARNING**; **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**; **Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis**; and **PRECAUTIONS:** *Use in Patients with Concomitant Illness*). The safety and efficacy of ABILIFY (aripiprazole) in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 7951 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5235 patient-years of exposure. A total of 2280 aripiprazole-treated patients were treated for at least 180 days and 1558 aripiprazole-treated patients had at least 1 year of exposure.

The conditions and duration of treatment with aripiprazole included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing 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. There was no attempt to use investigator causality assessments; ie, all reported events are included.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors 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 treatment, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Schizophrenia

The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which aripiprazole was administered in doses ranging from 2 to 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole- and placebo-treated patients.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

The following findings are based on a pool of 3-week, placebo-controlled, bipolar mania trials in which aripiprazole was administered at doses of 15 or 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, in patients with bipolar mania, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (11%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

Commonly observed adverse events associated with the use of aripiprazole in patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 1. There were no adverse events in the short-term trials of schizophrenia that met these criteria.

Table 1: Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

	Percentage of Patients Reporting Event	
Adverse Event	Aripiprazole (n=597)	Placebo (n=436)
Accidental Injury	6	3
Constipation	13	6
Akathisia	15	4

Adverse Events Occurring at an Incidence of 2% or More Among Aripiprazole-Treated Patients and Greater than Placebo in Short-Term, Placebo-Controlled Trials

Table 2 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 2: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials

	Percentage of Patients Reporting Event[a]	
Body System Adverse Event	Aripiprazole (n=1523)	Placebo (n=849)
Body as a Whole		
Headache	31	26
Asthenia	8	7
Accidental Injury	5	4
Peripheral Edema	2	1
Cardiovascular System		
Hypertension	2	1
Digestive System		
Nausea	16	12
Dyspepsia	15	13
Vomiting	11	6
Constipation	11	7
Musculoskeletal System		
Myalgia	4	3
Nervous System		
Agitation	25	24
Anxiety	20	17
Insomnia	20	15
Somnolence	12	8
Akathisia	12	5
Lightheadedness	11	8
Extrapyramidal Syndrome	6	4
Tremor	4	3
Increased Salivation	3	1
Respiratory System		
Pharyngitis	4	3
Rhinitis	4	3
Coughing	3	2
Special Senses		
Blurred Vision	3	1

[a] Events reported by at least 2% of patients treated with aripiprazole, except the following events, which had an incidence equal to or less than placebo: abdominal pain, back pain, dental pain, diarrhea, dry mouth, anorexia, psychosis, hypertonia, upper respiratory tract infection, rash, vaginitis[f], dysmenorrhea[f].

[f] Percentage based on gender total.

An examination of population subgroups did not reveal any clear evidence of differential adverse event incidence on the basis of age, gender, or race.

Dose-Related Adverse Events

Schizophrenia

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, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 17% vs. 12% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the bipolar mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

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%).

Table 3 provides the weight change results from a long-term (26-week), placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 3: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample

	BMI <23		BMI 23-27		BMI >27	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
Mean change from baseline (kg)	-0.5	-0.5	-0.6	-1.3	-1.5	-2.1
% with ≥7% increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

Table 4 provides the weight change results from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 4: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample

	BMI <23	BMI 23-27	BMI >27
Mean change from baseline (kg)	2.6	1.4	-1.2
% with ≥7% increase BW	30%	19%	8%

ECG Changes

Between group comparisons for a pooled analysis of placebo-controlled trials in patients with schizophrenia or bipolar mania, revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. 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.[55]

Additional Findings Observed in Clinical Trials

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

The adverse events reported in a 26-week, double-blind trial comparing ABILIFY (aripiprazole) and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9% (13/153) for ABILIFY vs. 1% (2/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days), and were of limited duration (9/13 ≤10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for ABILIFY was 4% (34/859). A similar adverse event profile was observed in a long-term study in bipolar disorder.

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 7951 patients. All reported events are included except those already listed in Table 2, or other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent – flu syndrome, fever, chest pain, rigidity (including neck and extremity), neck pain, pelvic pain; *Infrequent* – face edema, suicide attempt, malaise, migraine, chills, photosensitivity, tightness (including abdomen, back, extremity, head, jaw, neck, and tongue), jaw pain, bloating, enlarged abdomen, chest tightness, throat pain; *Rare* – moniliasis, head heaviness, throat tightness, Mendelson's syndrome, heat stroke.

Cardiovascular System: Frequent – tachycardia (including ventricular and supraventricular), hypotension, bradycardia; *Infrequent* – palpitation, hemorrhage, heart failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris, pallor, cardiopulmonary arrest, phlebitis; *Rare* – bundle branch block, atrial flutter, vasovagal reaction, cardiomegaly, thrombophlebitis, cardiopulmonary failure.

Digestive System: Frequent – nausea and vomiting; *Infrequent* – increased appetite, dysphagia, gastroenteritis, flatulence, tooth caries, gastritis, gingivitis, gastrointestinal hemorrhage, hemorrhoids, gastroesophageal reflux, periodontal abscess, fecal incontinence, rectal hemorrhage, stomatitis, colitis, tongue edema, cholecystitis, mouth ulcer, oral moniliasis, eructation, fecal impaction, cholelithiasis; *Rare* – esophagitis, hematemesis, intestinal obstruction, gum hemorrhage, hepatitis, peptic ulcer, glossitis, melena, duodenal ulcer, cheilitis, hepatomegaly, pancreatitis.

Endocrine System: Infrequent – hypothyroidism; *Rare* – goiter, hyperthyroidism.

Hemic/Lymphatic System: Frequent – ecchymosis, anemia; *Infrequent* – hypochromic anemia, leukocytosis, leukopenia (including neutropenia), lymphadenopathy, eosinophilia, macrocytic anemia; *Rare* – thrombocythemia, thrombocytopenia, petechiae.

Metabolic and Nutritional Disorders: Frequent – weight loss, creatine phosphokinase increased, dehydration; *Infrequent* – edema, hyperglycemia, hypercholesteremia, hypokalemia, diabetes mellitus, hypoglycemia, hyperlipemia, SGPT increased, thirst, BUN increased, hyponatremia, SGOT increased, creatinine increased, cyanosis, alkaline phosphatase increased, bilirubinemia, iron deficiency anemia, hyperkalemia, hyperuricemia, obesity; *Rare* – lactic dehydrogenase increased, hypernatremia, gout, hypoglycemic reaction.

Musculoskeletal System: Frequent – muscle cramp; *Infrequent* – arthralgia, myasthenia, arthrosis, bone pain, arthritis, muscle weakness, spasm, bursitis, myopathy; *Rare* – rheumatoid arthritis, rhabdomyolysis, tendonitis, tenosynovitis.

Nervous System: Frequent – depression, nervousness, schizophrenic reaction, hallucination, hostility, confusion, paranoid reaction, suicidal thought, abnormal gait, manic reaction, delusions, abnormal dream; *Infrequent* – emotional lability, twitch, cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence, extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, panic attack, decreased libido, hypersomnia, dyskinesia, manic depressive reaction, ataxia, visual hallucination, cerebrovascular accident, hypokinesia, depersonalization, impaired memory, delirium, dysarthria, tardive dyskinesia, amnesia, hyperactivity, increased libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia, increased reflexes, akinesia, decreased consciousness, hyperesthesia, slowed thinking; *Rare* – blunted affect, euphoria, incoordination, oculogyric crisis, obsessive thought, hypotonia, buccoglossal syndrome, decreased reflexes, derealization, intracranial hemorrhage.

Respiratory System: Frequent – sinusitis, dyspnea, pneumonia, asthma; *Infrequent* – epistaxis, hiccup, laryngitis, aspiration pneumonia; *Rare* – pulmonary edema, increased sputum, pulmonary embolism, hypoxia, respiratory failure, apnea, dry nasal passages, hemoptysis.

Skin and Appendages: Frequent – skin ulcer, sweating, dry skin; *Infrequent* – pruritus, vesiculobullous rash, acne, eczema, skin discoloration, alopecia, seborrhea, psoriasis; *Rare* – maculopapular rash, exfoliative dermatitis, urticaria.

Special Senses: Frequent – conjunctivitis; *Infrequent* – ear pain, dry eye, eye pain, tinnitus, cataract, otitis media, altered taste, blepharitis, eye hemorrhage, deafness; *Rare* – diplopia, frequent blinking, ptosis, otitis externa, amblyopia, photophobia.

Urogenital System: Frequent – urinary incontinence; *Infrequent* – urinary frequency, leukorrhea, urinary retention, cystitis, hematuria, dysuria, amenorrhea, vaginal hemorrhage, abnormal ejaculation, kidney failure, vaginal moniliasis, urinary urgency, gynecomastia, kidney calculus, albuminuria, breast pain, urinary burning; *Rare* – nocturia, polyuria, menorrhagia, anorgasmy, glycosuria, cervicitis, uterus hemorrhage, female lactation, urolithiasis, priapism.

Other Events Observed During the Postmarketing Evaluation of Aripiprazole

Voluntary reports of adverse events in patients taking aripiprazole that have been received since market introduction and not listed above that may have no causal relationship with the drug include rare occurrences of allergic reaction (e.g., anaphylactic reaction, angioedema, laryngospasm, pruritus, or urticaria).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILIFY (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. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and 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. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

MedDRA terminology has been used to classify the adverse events.

Human Experience

A total of 76 cases of deliberate or accidental overdosage with aripiprazole have been reported worldwide. These include overdoses with aripiprazole alone and in combination with other substances. No fatality was reported from these cases. Of the 44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (mydriasis and feeling abnormal). The largest known acute ingestion with a known outcome involved 1080 mg of aripiprazole (36 times the maximum recommended daily dose) in a patient who fully recovered. Included in the 76 cases are 10 cases of deliberate or accidental overdosage in children (age 12 and younger) involving aripiprazole ingestions up to 195 mg with no fatalities.

Common adverse events (reported in at least 5% of all overdose cases) reported with aripiprazole overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

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
Orally disintegrating tablets manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Oral Solution manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA
Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
US Patent Nos: 5,006,528 and 6,977,257

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University of Illinois at Chicago (UIC)

The University of Illinois at Chicago College of Medicine invites applicants and nominations for the position of Head of the Department of Psychiatry. The Department is a national leader, ranked 17th in NIH funding, first in Illinois, and second in the Midwest. The Department includes five subspecialty programs: Child Psychiatry, Mood & Anxiety Disorders, Neurobehavior, Psychosis, and Women's Mental Health.

Department faculty have achieved national recognition for research, clinical services and training programs in many areas, including: autism; biological substrate of suicide; childhood bipolar disorder; neurobiology of alcoholism; neurobiology of depression; neurobiology & prevention of schizophrenia; neurosteroids, GABA & psychopathology; oxytocin and behavior; perinatal depression; psychiatric effects of HIV infection; psychosocial rehabilitation; sex hormones & cognition; youth violence; and, workplace harassment. The department is home to three institutes, the Institute for Juvenile Research, the Neuropsychiatric Institute and the Psychiatric Institute, and seven centers, including a National Research and Training Center for Psychiatric Disabilities, the Center for Cognitive Medicine, and the Brain-Body Center. The department has 108 full time faculty members, a well-established residency program, and a large in- and out-patient base.

The ideal candidate will be board certified in Psychiatry, have a history of established extramurally funded research, experience in administration of both basic and clinical science programs, is a nationally known, respected academician, and have had successful experience with complex organizations and collaborative work environments.

For fullest consideration, nominations and/or letters of application, along with CV and three letters of reference, should be submitted by December 31, 2006 to:

Dimitri T. Azar, MD, Field Chair of Ophthalmologic Research
Professor and Head, Chair of the Head of Psychiatry Search Committee
University of Illinois at Chicago
Department of Ophthalmology and Visual Sciences
MC 648, 1855 West Taylor Street
Chicago, IL, 60612
Email: dazar@uic.edu

UIC IS AN AFFIRMATIVE ACTION / EQUAL OPPORTUNITY EMPLOYER

Albany Medical College

The Department of Psychiatry seeks a Board Eligible/Board Certified psychiatrist. ECT training and competence preferred. The department's multi-disciplinary teams include a resident, 2-3 medical students, psychologists, social workers, recreational therapists & occupational therapists. The position offers an academic appointment and opportunities for creative development and administration, if interested. Occasional call coverage may be necessary. The inpatient psychiatry unit at AMC started in 1902 and is the oldest continuously operating unit in a general hospital in the country. The unit is closed and has 52 beds on 2 floors. Albany boasts seven colleges and universities and enjoys a rich collection of arts and entertainment venues. Enjoy boating on the Hudson or nearby ski resorts. Less than three hours to Boston, New York City and Montreal.

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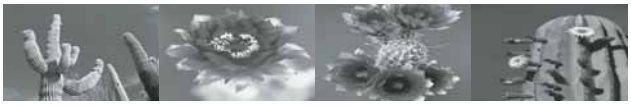

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Send CV to: Physician Recruitment, HPMG, Dole Cannery Square, 501 Alakawa Street, Suite 255, Honolulu, Hawaii 96817-5764, Fax (808) 432-4620 or email: Janice.Omori@kp.org.

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DEPARTMENT OF VETERANS AFFAIRS MEDICAL CENTER DAYTON, OHIO

The Department of Veterans Affairs Medical Center, Dayton, Ohio, seeks a Psychiatrist to provide direct patient care within a 115 bed Residential Rehabilitation Program. Substance Abuse is one area of focus. The Medical Center is a 539-bed multi-specialty Dean's Committee Hospital. Faculty appointments and research support are available to qualified applicants.

Applicants should be board-certified or board eligible. Graduating residents and fellows may apply; have a license from one of the 50 states; and be a citizen or permanent resident or the USA.

Competitive Salary
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Dayton, the birthplace of flight, is located in the beautiful rolling hills of Southwestern Ohio and offers the convenience of a city without the hassles. The metropolitan area has five universities, good school systems, museums, theaters, and other recreational opportunities, and is the home of Wright-Patterson Air Force Base.

Send curriculum vitae with three references to:

William F. O'Brien, Ph.D.
Manager, Mental Health Care Line
Dayton VA Medical Center
4100 West Third Street
Dayton, OH 45428
E-mail: William.Obrien@med.va.gov
Tel: 937-268-6511, ext. 2667, Fax: 937-267-3924

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Director of the VISN 6 MIRECC

Department of Veterans Affairs

The U.S. Department of Veterans Affairs (VA) Mid-Atlantic Mental Illness Research, Education, and Clinical Center (MIRECC) invites applications for the position of MIRECC Director. The Director will maintain the MIRECC's focus on post-deployment mental health with emphasis on the patient registry as a population for longitudinal research. A successful candidate will be eligible to serve as a mental health provider in the Department of Veterans Affairs facilities and eligible for appointment at the rank of Associate Professor or higher in the Department of Psychiatry and Behavioral Sciences at Duke University Medical Center.

The Veterans Health Administration is the largest integrated health care system in the nation, and the VISN 6 MIRECC was established in 2004 with a hub site at the Durham VA Medical Center within the VISN 6 VA Healthcare System, with its Director and administrative leadership located in Durham, North Carolina. The Center facilitates and enables research through support of core activities and ongoing initiatives in areas of high clinical relevance, as well as support of pilot studies and other research development activities. In addition, it conducts clinical and educational/training activities to facilitate the translation of research findings into clinical practice. The MIRECC serves as a resource for the VISN network liaison in mental health.

Applicants must hold an MD degree, a PhD degree in Psychology, Nursing, Social Work, or an equivalent degree. A successful candidate will also have experience in education and mentorship of developing clinicians and investigators; ability to work within interdisciplinary teams; a record of publication and competitive grant support in clinical, intervention, and/or health services research in the area of the MIRECC's focus; and a national or international reputation for leadership and productivity in this area. In evaluating candidates, expertise within these relevant areas will be considered, as well as the depth of their leadership experience and productivity.

Interested candidates should forward a statement of interest and a resume/curriculum vitae to:

Perry Whitted
Program Manager, Mid-Atlantic MIRECC
VA Medical Center
508 Fulton Street
Durham, NC 27705
Fax: (919) 416-5912
E-mail: Perry.Whitted@va.gov

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SEMEL INSTITUTE UCLA

UCLA Faculty Position in Psychoneuroimmunology

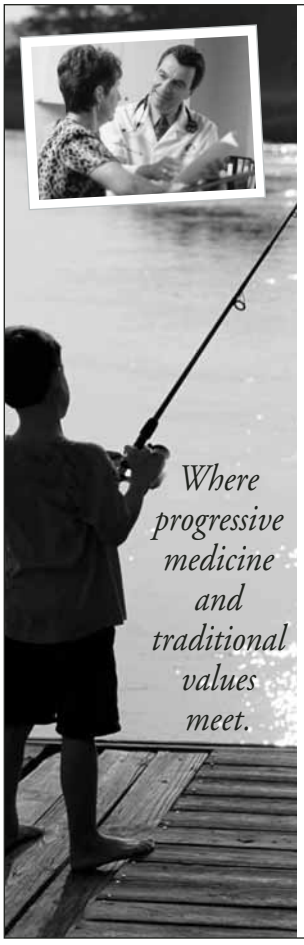
The Department of Psychiatry and Biobehavioral Sciences and the Jane and Terry Semel Institute for Neuroscience and Human Behavior (an interdisciplinary research and education institute devoted to the understanding of complex human behavior) at UCLA and the Cousins Center for Psychoneuroimmunology invite applications for a full time mid-career position with guaranteed base salary.

Qualifications: Scientist (M.D., Ph.D. preferred) with active collaborative research program and excellent publication record in the field of psychoneuroimmunology, with a preferred focus on aging or oncology. Expertise in molecular immunology is preferred, but other areas will be considered. Excellent teaching skills and the ability to train and mentor masters and doctoral students as well as junior faculty are required.

To apply, submit a letter of interest, curriculum vitae, representative reprints and names and addresses of three references (do not send letters) via email by December 1, 2006 to:

Cathey Heron (**cheron@mednet.ucla.edu**)
Search Coordinator
Psychoneuroimmunology Search Committee

UCLA is an EOE.



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Marshfield Clinic is a multi-specialty group practice with over 725 physicians located at 40 centers in Wisconsin. The Clinic's Research Foundation has a history of important medical discoveries in human genetics and support for clinical research.

To learn more about these opportunities and the very competitive compensation package, please contact: Beth Albee, Physician Recruitment, **Marshfield Clinic**, 1000 N. Oak Ave., Marshfield, WI 54449. Phone: 800-782-8581, extension 19775; Fax #: 715-221-9779.

E-mail: albee.beth@marshfieldclinic.org
Website: www.marshfieldclinic.org/recruit

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London Health Sciences Centre

DEPARTMENT OF PSYCHIATRY
LONDON HEALTH SCIENCES CENTRE, SOUTH STREET HOSPITAL
and
THE UNIVERSITY OF WESTERN ONTARIO
SCHULICH SCHOOL OF MEDICINE & DENTISTRY

CLINICAL ACADEMIC POSITION
STAFF PSYCHIATRIST, TRAUMATIC STRESS SERVICE

The Traumatic Stress Service (TSS), London Health Sciences Centre (LHSC), South Street Hospital, London, Ontario, Canada has a position available immediately for a staff psychiatrist with interest and experience in treating psychological trauma spectrum disorders in an outpatient, team setting. This position will report to the Physician Leader of the Traumatic Stress Program and to the Site Chief, Department of Psychiatry at LHSC.

The TSS is seeking a General Psychiatrist who is comfortable working in a multidisciplinary team environment. The successful applicant would be able to provide tertiary consultations and assess patients suffering from the sequelae of psychological trauma for admission to the program, and be familiar with treating trauma patients with a range of specific and general group and individual treatment models (e.g. DBT, CBT, EMDR). The successful candidate will also be comfortable admitting unstable TSS patients for brief stays and following them on the inpatient unit.

Although the position is primarily focused on clinical service, knowledge of program development and evaluation would be valuable. Moreover, because the TSS mandate is to provide clinical treatment, research and teaching for the trauma spectrum disorders, collaborative interest in linking with the research arm of the TSS is encouraged. Peer supervision, resident and medical student teaching and supervision, community education and local conference participation are also required in this position. The incumbent will be eligible for an academic appointment in the Schulich School of Medicine & Dentistry at an entry rank commensurate with experience and training. Candidates must hold an MD or equivalent and be eligible for academic certification in Psychiatry from the Royal College of Physicians and Surgeons of Canada or equivalent.

South Street Hospital is one of a number of hospitals and facilities in London, Ontario administered under the London Health Sciences Centre and affiliated with the Schulich School of Medicine & Dentistry, The University of Western Ontario. The London Health Sciences Centre is committed to having a racially and culturally diverse faculty. The clinical programs emphasize evidence-based practice and capacity building. In addition, the Department of Psychiatry provides an intellectually exciting, collegial, and supportive faculty environment that fosters interdisciplinary and international research.

Situated in the University town of London in South Western Ontario, London is a beautiful, old city offering a rich cultural and outdoor recreational environment, it is a one-hour drive from beautiful cottage country in Bayfield and Grand Bend on Lake Huron and, for ski enthusiasts, it is two hours from Collingwood, Ontario. London is also within driving distance of Stratford, approximately 1 hr 10 minutes, for theatre lovers. London's airport has recently become an international airport.

Interested candidates should submit a letter of inquiry, curriculum vita, names and addresses of three professional references to:
Ruth Lanius, MD PhD FRCPC; Director, Traumatic Stress Service; London Health Sciences Centre; 375 South Street; London, Ontario N6A 4G5

Applications will be accepted until an appropriate candidate is found.

Western

Positions are subject to budget approval. Applicants should have fluent written and oral communication skills in English. All qualified candidates are encouraged to apply; however Canadians and permanent residents will be given priority. The University of Western Ontario is committed to employment equity and welcomes applications from all qualified women and men, including visible minorities, aboriginal people and persons with disabilities.

Schulich MEDICINE & DENTISTRY

CLINICAL DIRECTOR

Mississippi State Hospital

Mississippi State Hospital is seeking a chief psychiatrist and administrator of psychiatric and medical care. The hospital is the largest public psychiatric facility in the U.S. and serves an average of 1,400 people daily through psychiatric, forensic, child-adolescent and chemical dependency services, the Jaquith Nursing Home, Community Services programs and Crisis Intervention Centers.

Located 15 minutes from downtown Jackson, the historic 350-acre facility features over 75 buildings, including a post office, a full-service cafeteria and a 32-bed medical surgical hospital. New service projects include the fall 2004 opening of two 50-bed acute psychiatric units at the main campus in Whitfield and two Crisis Intervention Centers in Cleveland and Grenada. A third center under construction in Brookhaven is scheduled to open in May 2007.

We are seeking applicants who are board certified in psychiatry and have two or more years of experience in psychiatric administration. Strong leadership abilities and superior communication skills are prerequisites. The position offers personal and medical leave, health insurance, participation in the state of Mississippi retirement plan and other valuable benefits.

Confidential requests for information and application materials should be directed to: Vicki Dunaway
Mississippi State Hospital, P.O. Box 157-A, B-61
Whitfield, MS 39193
(601) 351-8445; (601) 351-8415
dunawvi@msh.state.ms.us

For more information, visit http://www.msh.state.ms.us/ClinicalDirector
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ANXIETY PHARMACOTHERAPY & FUNCTIONAL NEUROIMAGING

The University of California San Diego (UCSD) in La Jolla, CA, is seeking applicants for a PGY-5 Anxiety Pharmacotherapy & Functional Neuroimaging Fellowship starting July 1, 2007.

Fellows have an opportunity to develop expertise in anxiety disorders outcomes research and functional magnetic resonance imaging (fMRI) task design and analysis. Dual mentorship by Martin P. Paulus MD and Murray B. Stein MD, MPH.

Competitive salary.
Two-year commitment preferred.

Applicants must be board-eligible in psychiatry and eligible for California medical licensure.

Interested candidates should send a CV and statement of interest by e-mail:

Dr. Stein (mstein@ucsd.edu) and/or
Dr. Paulus (mpaulus@ucsd.edu).

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BILOXI/PENSACOLA Send applications to Bridget Gehlsen, VAMC, HRMS (05A), 400 Veterans Ave, Biloxi MS or contact at bridget.gehlsen@med.va.gov or (228) 523-5633

ALEXANDRIA Strong clinical skills/team oriented. Located in the heart of LA. 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 Contact Vicla Johnson at (318) 221-8411, ext 7109 or vicla.johnson@med.va or send your CV by email or mail it to VAMC, HRMS (05), 510 E. Stoner Ave, Shreveport LA or (318) 221-8411, ext 7109

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

JOIN THE NEW VA! NORTHEAST OHIO

Louis Stokes Cleveland VA Medical Center a teaching affiliate of Case Western Reserve University (CWRU) seeks quality board certified applicants for full-time Psychiatric positions in expanding mental health network throughout Northeast Ohio including Akron, Canton, East Liverpool, Lorain, Mansfield, McCafferty, New Philadelphia, Painesville, Ravenna, Sandusky Warren and Youngstown.

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Scott K. Ober, MD, MBA
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Psychiatrist

Working in Social and Behavioral Health Services, conduct biopsychosocial assessments of pain management program patients and develop comprehensive interdisciplinary treatment plans in coordination with the primary care provider and patient. Requires experience in a full range of psychosocial interventions, techniques, and services to enhance or serve as adjunct therapy to medication for chronic pain. Requires a current, active and unrestricted state license to practice as a medical physician (psychiatrist), US citizenship and proficiency in written and spoken English.

Anchorage offers plenty of opportunity to take in salmon fishing, the arts, or the simplicity of peace and natural serenity. We offer comprehensive benefits, including generous leave, tuition reimbursement, a 24 percent tax deferred cost of living adjustment, and Alaska has no sales or income tax. For a complete job description and application information, please visit **www.usajobs.opm.gov, or call Robert Jerdan, HR Specialist, at: (907) 257-5453**. To apply, please send your completed application to: **Human Resources, AVAHSRO, 2925 DeBarr Road, Anchorage, AK 99508.**

Alaska Healthcare System and Regional Office

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Position offers a competitive salary guarantee. In addition, there is bonus potential and a full array of benefits including health, dental, vision, life and disability insurance, malpractice, CME, vacation, retirement, and relocation.

SPRINGFIELD, MISSOURI, (pop. 200,000) is a growing, sophisticated community. It is home to Missouri's second largest university and a regional home to the arts (symphony, ballet, and theater) and NCAA and semi-professional sports teams (football, basketball, baseball, and hockey). *Employment Review* has named Springfield one of the 10 "*Best Places to Live and Work*" in the U.S. For more information about Springfield, go to *www.springfieldmo.org*. EOE/AA Employer.

For more information, contact:

Julie Oliver, Physician Recruiter
St. John's Clinic
1965 S. Fremont, Suite 320
Springfield, MO 65804
Phone: (800) 218-5079; Fax: (888) 290-8300
jaoliver@sprg.mercy.net

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 200/75).

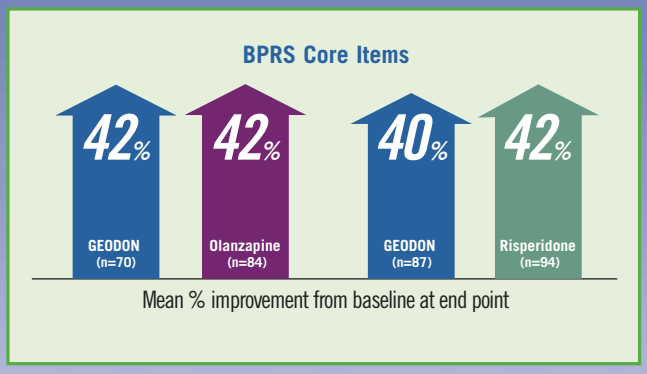
References: 1. Data on file. Pfizer Inc., New York, NY. **2.** Simpson GM, Glick ID, Weiden PJ, Romano SJ, Siu CO. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective 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 May 2005

Treat schizophrenia with the body in mind

COMPARABLE EFFICACY

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

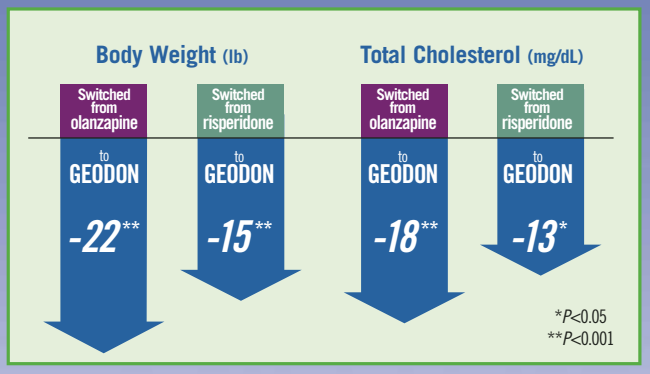


A 6-week, double-blind, randomized study of GEODON vs olanzapine and an 8-week, double-blind, randomized study of GEODON vs risperidone.

- 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[1,5]



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

- Patients switching to GEODON from olanzapine and risperidone also experienced reductions in triglycerides[5]

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®
(ziprasidone HCl) Oral Capsules

GEODON is indicated for the treatment of schizophrenia and of acute manic or mixed episodes associated with bipolar disorder.

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%).

Please see brief summary of prescribing information on adjacent page.

Pfizer NEUROSCIENCE