JANUARY 2008 VOLUME 13 — NUMBER 1

CNS SPECTRUMS®

THE INTERNATIONAL JOURNAL OF NEUROPSYCHIATRIC MEDICINE

Index Medicus/MEDLINE citation: ***CNS Spectr***

www.cnsspectrums.com

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press

Vyvanse™ (lisdexamfetamine dimesylate) **CII** **Rx Only**

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

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

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

INDICATIONS AND USAGE

Vyvanse is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

The efficacy of Vyvanse in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, who met DSM-IV® criteria for ADHD (see CLINICAL TRIALS).

A diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD; DSM-IV®) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, in social, academic, or occupational functioning, and be present in two or more settings, e.g., at school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: *fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go"; excessive talking; blurting* answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

Special Diagnostic Considerations: Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV® characteristics.

Need for Comprehensive Treatment Program: Vyvanse is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Long-Term Use: The effectiveness of Vyvanse for long-term use, i.e., for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Vyvanse for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Serious Cardiovascular Events

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

Children and Adolescents

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

Adults

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

Hypertension and other Cardiovascular Conditions

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

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

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

Psychiatric Adverse Events

Pre-Existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with pre-existing psychotic disorder.

Bipolar Illness

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

Emergence of New Psychotic or Manic Symptoms

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

Aggression

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

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of amphetamine (d to l enantiomer ratio of 3:1) in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was –1.1 lbs. and –2.8 lbs., respectively, for patients receiving 10 mg and 20 mg of amphetamine (d to l enantiomer ratio of 3:1). Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. In a controlled trial of lisdexamfetamine in children ages 6 to 12 years, mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.9, and -2.5 lb, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of lisdexamfetamine, compared to a 1 lb weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Careful follow-up for weight in children ages 6 to 12 years who received lisdexamfetamine over 12 months suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a slowing in growth rate measured by body weight as demonstrated by an age- and sex-normalized mean change from baseline in percentile of -13.4 over 1 year (average percentile at baseline and 12 months were 60.6 and 47.2, respectively). Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

Seizures

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

Visual Disturbance

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

PRECAUTIONS

General: The least amount of Vyvanse feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Vyvanse should be used with caution in patients who use other sympathomimetic drugs.

Tics: Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with lisdexamfetamine and should counsel them in its appropriate use. A patient Medication Guide is available for Vyvanse. 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.

Drug Interactions:

Urinary acidifying agents — These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

Adrenergic blockers — Adrenergic blockers are inhibited by amphetamines.

Antidepressants, tricyclic — Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO inhibitors — MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve *endings; this can cause headaches and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant* hyperpyrexia can occur, sometimes with fatal results.

Antihistamines — Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives — Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine — Chlorpromazine blocks dopamine and norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines and can be used to treat amphetamine poisoning.

Ethosuximide — Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol — Haloperidol blocks dopamine receptors, thus inhibiting the central stimulant effects of amphetamines.

Lithium carbonate — The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meperidine — Amphetamines potentiate the analgesic effect of meperidine.

Methenamine therapy — Urinary excretion of amphetamines is increased, and efficacy is reduced by acidifying agents used in methenamine therapy.

Norepinephrine — Amphetamines enhance the adrenergic effect of norepinephrine.

Phenobarbital — Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin — Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene — In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum alkaloids — Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis and Impairment of Fertility: Carcinogenicity studies of lisdexamfetamine have not been performed.

No evidence of carcinogenicity was found in studies in which d, l-amphetamine (enantiomer ratio of 1:1) was administered to mice and rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. Lisdexamfetamine dimesylate was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* and *S. typhimurium* components of the Ames test and in the L5178Y/TK+/- mouse lymphoma assay *in vitro*.

Amphetamine (d to l enantiomer ratio of 3:1) did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day.

Pregnancy: Pregnancy Category C. Reproduction studies of lisdexamfetamine have not been performed.

Amphetamine (d to l enantiomer ratio of 3:1) had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 16 mg/kg/day, respectively. Fetal malformations and death have been reported in mice following parenteral administration of dextroamphetamine doses of 50 mg/kg/day or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity.

A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or d,l-) at doses similar to those used clinically can result in long term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamine have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Usage in Nursing Mothers: *Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from* nursing.

Pediatric Use: Vyvanse is indicated for use in children aged 6 to 12 years.

A study was conducted in which juvenile rats received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine from day 7 to day 63 of age. These doses are approximately 0.3, 0.7, and 3 times the maximum recommended human daily dose of 70 mg on a mg/m^2 basis. Dose-related decreases in food consumption, bodyweight gain, and crown-rump length were seen; after a four week drug-free recovery period bodyweights and crown-rump lengths had significantly recovered in females but were still substantially reduced in males. Time to vaginal opening was delayed in females at the highest dose, but there were no drug effects on fertility when the animals were mated beginning on day 85 of age.

In a study in which juvenile dogs received lisdexamfetamine for 6 months beginning at 10 weeks of age, decreased bodyweight gain was seen at all doses tested (2, 5, and 12 mg/kg/day, which are approximately 0.5, 1, and 3 times the maximum recommended human daily dose on a *mg/m^2 basis). This effect partially or fully reversed during a four week drug-free recovery period.*

Use in Children under Six Years of Age: Lisdexamfetamine dimesylate has not been studied in 3-5 year olds. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age.

Geriatric Use: Vyvanse has not been studied in the geriatric population.

ADVERSE EVENTS

The premarketing development program for Vyvanse included exposures in a total of 404 participants in clinical trials (348 pediatric patients and 56 healthy adult subjects). Of these, 348 pediatric patients (ages 6 to 12) were evaluated in two controlled clinical studies (one parallel-group and one crossover), one open-label extension study, and one single-dose clinical pharmacology study. The information included in this section is based on data from the 4-week parallel-group controlled clinical trial in pediatric patients with ADHD. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of *their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing* adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, MedRA terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed.

Adverse events associated with discontinuation of treatment: Ten percent (21/218) of Vyvanse-treated patients discontinued due to adverse events compared to 1% (1/72) who received placebo. The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, and rash (2/218 each; 1%).

Adverse events occurring in a controlled trial: Adverse events reported in a 4-week clinical trial in pediatric patients treated with Vyvanse or placebo are presented in the table below.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The following adverse events that occurred in at least 5% of the Vyvanse patients and at a rate twice that of the placebo group (Table 1): Upper abdominal pain, decreased appetite, dizziness, dry mouth, irritability, insomnia, nausea, vomiting, and decreased weight.

Table 1 Adverse Events Reported by 2% or More of Pediatric Patients Taking Vyvanse in a 4 Week Clinical Trial

Body System	Preferred Term	Vyvanse (*n=218*)	Placebo (*n=72*)
Gastrointestinal Disorders	Abdominal Pain Upper	12%	6%
	Dry Mouth	5%	0%
	Nausea	6%	3%
	Vomiting	9%	4%
General Disorder and Administration Site Conditions	Pyrexia	2%	1%
Investigations	Weight Decreased	9%	1%
Metabolism and Nutrition	Decreased Appetite	39%	4%
Nervous System Disorders	Dizziness	5%	0%
	Headache	12%	10%
	Somnolence	2%	1%
Psychiatric Disorders	Affect lability	3%	0%
	Initial Insomnia	4%	0%
	Insomnia	19%	3%
	Irritability	10%	0%
	Tic	2%	0%
Skin and Subcutaneous Tissue Disorders	Rash	3%	0%

Note: This table only includes those events for which the incidence in patients taking Vyvanse is greater than the incidence in patients taking placebo.

The following additional adverse reactions have been associated with the use of amphetamine, amphetamine (d to l enantiomer ratio of 3:1), or Vyvanse:

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation.

Allergic: Urticaria, hypersensitivity reactions including angioedema and anaphylaxis. Serious skin rashes, including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Vyvanse is classified as a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to levels many times higher than recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

Human Studies

In a human abuse liability study, when equivalent oral doses of 100 mg lisdexamfetamine dimesylate and 40 mg immediate release d-amphetamine sulfate were administered to individuals with a history of drug abuse, lisdexamfetamine 100 mg produced subjective responses on a scale of "Drug Liking Effects" "Amphetamine Effects", and "Stimulant Effects" that were significantly less than d-amphetamine immediate release 40 mg. However, oral administration of 150 mg lisdexamfetamine produced increases in positive subjective responses on these scales that were statistically indistinguishable from the positive subjective responses produced by 40 mg of oral immediate-release d-amphetamine and 200 mg of diethylpropion (C-IV).

Intravenous administration of 50 mg lisdexamfetamine to individuals with a history of drug abuse produced positive subjective responses on scales measuring "Drug Liking", "Euphoria", "Amphetamine Effects", and "Benzedrine Effects" that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.

Animal Studies

In animal studies, lisdexamfetamine produced behavioral effects qualitatively similar to those of the CNS stimulant d-amphetamine. In monkeys trained to self-administer cocaine, intravenous lisdexamfetamine maintained self-administration at a rate that was statistically less than that for cocaine, but greater than that of placebo.

OVERDOSAGE

Individual response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Symptoms: Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment: Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

The prolonged release of Vyvanse in the body should be considered when treating patients with overdose.

Manufactured for: New River Pharmaceuticals Inc., Blacksburg, VA 24060. Made in USA.
Distributed by: Shire US Inc., Wayne, PA 19087
For more information call 1-800-828-2088, or visit www.Vyvanse.com

Rev 02/07 104A 04 LDX8S1

Shire

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press

Volume 13 — CNS SPECTRUMS® — Number 1

The International Journal of Neuropsychiatric Medicine

EDITOR'S LETTER

INTRODUCTION

REVIEW ARTICLES

ORIGINAL RESEARCH

Founded in 1996, *CNS Spectrums* is indexed in the *Index Medicus* database and is available on MEDLINE under the citation *CNS Spectr*. *CNS Spectrums* is also the largest, peer-reviewed, indexed neuropsychiatric journal in the United States.

For editorial inquiries, please fax us at 212-328-0600 or e-mail José Ralat at jrr@mblcommunications.com. For bulk reprint purchases, please contact Christopher Naccari at cdn@mblcommunications.com.

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

One-year subscription rates: domestic $120; foreign $195; in-training $85. For subscriptions: Tel: 212-328-0800, Fax: 212-328-0600; Web: www.cns-spectrums.com. Single issues: $15 – e-mail ks@mblcommunications.com

Subscribers: send address changes to *CNS Spectrums* c/o MMS, Inc., 185 Hansen Court, Suite 110, Wood Dale, IL 60191-1150.

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press

Manage the diabetic peripheral neuropathic pain (DPNP) symptoms your patients talk about, and those they don't. Many times, patients don't mention some of their symptoms because they don't realize they are related. That's where Cymbalta can help. Cymbalta provides relief from the dominant symptoms of DPNP and may help relieve underlying symptoms, allowing you to treat patients more completely. To learn more about treating beyond the obvious, visit www.insidecymbalta.com

In pooled analysis and in individual studies, Cymbalta produced a significant separation ($P<.05$) from placebo on the weekly mean 24-hour average pain score at 12 weeks, the primary outcome of the study.

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

Important Safety Information

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

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

Clinical worsening and suicide risk: All patients being treated with an antidepressant for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially within the first few months of treatment and when changing the dose. A health professional should be immediately notified if the depression is persistently worse or there are symptoms that are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication.

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

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

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

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

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

As observed in DPNP clinical trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases up to 52 weeks, an increase in HbA_{1c} in both the Cymbalta (0.5%) and routine care groups (0.2%) was noted.

Most common adverse events (≥5% and at least twice placebo) in premarketing clinical trials were:
MDD: nausea, dry mouth, constipation, fatigue, decreased appetite, somnolence, and increased sweating. **DPNP:** nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia. **GAD:** nausea, fatigue, dry mouth, somnolence, constipation, insomnia, appetite decreased, increased sweating, libido decreased, vomiting, ejaculation delayed, and erectile dysfunction.

See Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent page.

Lilly

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press

CYMBALTA®
(duloxetine hydrochloride) Delayed-release Capsules

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

WARNING

Suicidality and Antidepressant Drugs-Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Cymbalta is not approved for use in pediatric patients.

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

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

WARNINGS: Clinical Worsening and Suicide Risk—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk of differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

Table 1

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

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

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

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

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

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

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

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

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

MAOIs—In patients receiving a serotonin reuptake inhibitor (SSRI) in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRIs and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of Cymbalta and MAOIs have not been evaluated in humans or animals. Therefore, because Cymbalta is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that Cymbalta not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of Cymbalta, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

Serotonin Syndrome—The development of a potentially life-threatening serotonin syndrome may occur with SNRIs and SSRIs, including Cymbalta treatment, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea).

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

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* PRECAUTIONS, Drug Interactions).

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

PRECAUTIONS: ***General***—Hepatotoxicity—Cymbalta increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.4% (31/8454) of Cymbalta-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to >3 times the upper limit of normal occurred in 0.9% (8/930) of Cymbalta-treated patients and in 0.3% (2/652) of placebo-treated patients. In controlled trials in DPN, elevations of ALT to >3 times the upper limit of normal occurred in 1.68% (8/477) of Cymbalta-treated patients and in 0% (0/187) of placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, elevation of ALT > 3 times the upper limit of normal occurred in 1% (39/3732) of Cymbalta-treated patients compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively. Postmarketing reports have described cases of hepatitis with abdominal pain, hepatomegaly and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. In clinical trials, three Cymbalta patients had elevations of transaminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Two placebo-treated patients also had transaminase elevations with elevated bilirubin. Postmarketing reports indicate that elevated transaminases, bilirubin and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis. Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease. Orthostatic Hypotension and Syncope—Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors (*see* CLINICAL PHARMACOLOGY, Drug-Drug Interactions, *and* PRECAUTIONS, Drug Interactions) and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy. Effect on Blood Pressure—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg BID. At the highest 200 mg BID dose, the increase in mean pulse rate was 5.0-6.8 bpm and increases in mean blood pressure were 4.7-6.8 mm Hg (systolic) and 4.5-7 mm Hg (diastolic) up to 12 hours after dosing. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes). Activation of Mania/Hypomania—In placebo-controlled trials in patients with MDD, activation of mania or hypomania was reported in 0.1% (2/2327) of duloxetine-treated patients and 0.1% (1/1460) of placebo-treated patients. No activation of mania or hypomania was reported in DPNP or GAD placebo-controlled trials. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of MDD. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania. Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.04% (3/8504) of patients treated with duloxetine and 0.02% (1/6123) of placebo-treated patients. Cymbalta should be prescribed with care in patients with a history of a seizure disorder. Hyponatremia—Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported and appeared to be reversible when Cymbalta was discontinued. Some cases were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in elderly individuals, some in patients taking diuretics or who were otherwise volume depleted. Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma (*see* CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma). Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt discontinuation in placebo-controlled clinical trials, the following symptoms occurred at a rate greater than or equal to 1% and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; nightmares; insomnia; diarrhea; anxiety; hyperhidrosis; and vertigo.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics). Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta and by 0.2% in the routine care groups. Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis). For this reason, Cymbalta is not recommended for patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and Cymbalta should not be administered to these patients.

Laboratory Tests—No specific laboratory tests are recommended.

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

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

Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules PV 5904 AMP

Serotonin Syndrome). The concomitant use of Cymbalta with other SSRIs, SNRIs, or tryptophan is not recommended (*see* PRECAUTIONS, Drug Interactions). Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (*see* WARNINGS, Serotonin Syndrome). Potential for Interaction with Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely *acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is* advised in using Cymbalta in patients with conditions that may slow gastric emptying (eg, some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq) or Cymbalta with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis). In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times *the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors. Mutagenesis—Duloxetine* was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*. Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at daily doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

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

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

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted *that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS, Monoamine Oxidase* Inhibitors). When treating a pregnant woman with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

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

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

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

Geriatric Use—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN premarketing studies, 33% (357) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD and DPN studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, Cymbalta has been associated with cases of clinically significant hyponatremia (*see* Hyponatremia, *under* PRECAUTIONS).

ADVERSE REACTIONS: Cymbalta has been evaluated for safety in 2418 patients diagnosed with MDD who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 Cymbalta-treated patients, 1139 patients participated in eight 8 or 9 week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated patients were exposed for at least 180 days and 445 Cymbalta-treated patients were exposed for at least 1 year. Cymbalta has also been evaluated for safety in 1074 patients with diabetic peripheral neuropathy representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated patients, 568 patients participated in two 12 to 13 week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with placebo, were exposed to Cymbalta for up to 12 months at 60 mg twice daily in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had 12 months of exposure.

Cymbalta has also been evaluated for safety in 668 patients with GAD representing 95 patient-years of exposure. These 668 patients participated in 9- or 10-week placebo-controlled trials at doses ranging from 60 to 120 mg once daily. Of these 668 patients, 449 were exposed for at least 2 months to Cymbalta.

In the full cohort of placebo-controlled clinical trials for any indication, safety has been evaluated in 8504 patients treated with duloxetine and 6123 patients treated with placebo. In clinical trials, a total of 23,983 patients have been exposed to duloxetine. In duloxetine clinical trials, adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

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

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a *treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the* first time or worsened while receiving therapy following baseline evaluation. Events reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 10% of the 1139 patients who received Cymbalta in the MDD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (Cymbalta 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo). Diabetic Peripheral Neuropathic Pain—Approximately 14% of the 568 patients who received Cymbalta in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients receiving placebo. Nausea (Cymbalta 3.5%, placebo 0.4%), dizziness (Cymbalta 1.6%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0%) and fatigue (Cymbalta 1.1%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo). Generalized Anxiety Disorder—Approximately 16% of the 668 patients who received Cymbalta in the GAD placebo-controlled trials discontinued treatment *due to an adverse event, compared with 4% of the 495 patients receiving placebo. Nausea (Cymbalta 3.7%, placebo* 0.2%), vomiting (Cymbalta 1.4%, placebo 0%), and dizziness (Cymbalta 1.2%, placebo 0.2%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials—Major Depressive Disorder—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of MDD placebo-controlled trials (N=1139 Cymbalta; N=777 placebo) with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, vomiting; Metabolism and Nutrition Disorders—appetite decreased (includes anorexia); Investigations—weight decreased; General Disorders and Administration Site Conditions—fatigue; Nervous System Disorders—dizziness, somnolence, tremors; Skin and Subcutaneous Tissue Disorders—sweating increased; Vascular Disorders—hot flushes; Eye Disorders—vision blurred; Psychiatric Disorders—insomnia (includes middle insomnia), anxiety, libido decreased, orgasm abnormal (includes anorgasmia); Reproductive System and Breast *Disorders—males only: erectile dysfunction, ejaculation delayed, ejaculatory dysfunction (includes ejaculation disorder and* ejaculation failure).

The following events were reported by at least 2% of patients treated with Cymbalta for MDD and had an incidence ≤ placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.

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

Diabetic Peripheral Neuropathic Pain—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of DPN placebo-controlled trials (N=225 Cymbalta 60 mg BID; N=228 Cymbalta 60 mg QD; N=115 Cymbalta 20 mg QD; N=223 placebo) with an incidence greater than placebo were: Gastrointestinal Disorders—nausea, constipation, diarrhea, dry mouth, vomiting, dyspepsia, loose stools; General Disorders and Administration Site Conditions—fatigue, asthenia, pyrexia; Infections and Infestations—nasopharyngitis; Metabolism and Nutrition Disorders—decreased appetite, anorexia; Musculoskeletal and Connective Tissue Disorders—muscle cramp, myalgia; Nervous System Disorders—somnolence, headache, dizziness, tremor; *Psychiatric Disorders—insomnia; Renal and Urinary Disorders—pollakiuria; Reproductive System and Breast* Disorders—erectile dysfunction; Respiratory, Thoracic and Mediastinal Disorders—cough, pharyngolaryngeal pain; Skin and Subcutaneous Tissue Disorders—hyperhidrosis.

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

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

Generalized Anxiety Disorder—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the premarketing acute phase of GAD placebo-controlled trials (doses of 60-120 mg once daily) (N=668 Cymbalta; N=495 placebo) and with an incidence greater than placebo were: Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, constipation, diarrhea, vomiting, abdominal pain, dyspepsia; General Disorders and Administration Site Conditions—fatigue; Metabolism and Nutrition Disorders—appetite decreased; Nervous System Disorders—dizziness, somnolence, tremor, paraesthesia; Psychiatric Disorders—insomnia, libido decreased, agitation, orgasm abnormal; Reproductive System and Breast Disorders—ejaculation delayed, erectile *dysfunction; Respiratory, Thoracic and Mediastinal Disorders—yawning; Skin and Subcutaneous Tissue Disorders*—hyperhidrosis; Vascular Disorders—hot flushes.

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

The most commonly observed adverse events in Cymbalta-treated GAD patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; fatigue; dry mouth; somnolence; constipation; insomnia; appetite decreased; hyperhidrosis; libido decreased; vomiting; ejaculation delayed; and erectile dysfunction.

Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of Cymbalta did not suggest a difference in adverse event rates in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if these patients responded differently from Caucasian patients.

Effects on Male and Female Sexual Function—Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance *and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss* them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Sexual side effects spontaneously reported by at least 2% of either male or female patients taking Cymbalta in MDD placebo-controlled trials were: Males (N=378 Cymbalta; N=247 placebo): orgasm abnormal (includes anorgasmia), ejaculatory dysfunction (includes ejaculation disorder and ejaculation failure), libido decreased, erectile dysfunction, ejaculation delayed. Females (N=761 Cymbalta; N=530 placebo): orgasm abnormal, libido decreased.

Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that there is no evidence that its effects differ from other antidepressants. *Physicians should routinely inquire about possible sexual side effects. See Table 5 in full PI for specific ASEX results.*

Urinary Hesitation—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related. ***Laboratory Changes***—Cymbalta treatment, for up to 9 weeks in MDD, 9-10 weeks in GAD, or 13 weeks in DPN placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients (*see* PRECAUTIONS). ***Vital Sign Changes***—In clinical trials across indications, relative to placebo, duloxetine treatment was associated with mean increases of up to 2.1 mm Hg in systolic blood pressure and up to 2.3 mm Hg in diastolic blood pressure, averaging up to 2 mm Hg. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure (*see* PRECAUTIONS). Duloxetine treatment, for up to 13 weeks in placebo-controlled trials typically caused a small increase in heart rate compared to placebo of up to 3 beats per minute. ***Weight Changes***—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10 weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13 weeks experienced a mean weight loss of *approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients.* ***Electrocardiogram Changes***—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13 weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg BID, no prolongation of the corrected QT interval was observed.

Postmarketing Spontaneous Reports—Adverse events reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, angioneurotic edema, erythema multiforme, extrapyramidal disorder, glaucoma, hallucinations, hyperglycemia, hypersensitivity, hypertensive crisis, rash, Stevens-Johnson Syndrome, supraventricular arrhythmia, trismus, and urticaria.

DRUG ABUSE AND DEPENDENCE: ***Controlled Substance Class***—Duloxetine is not a controlled substance. ***Physical and Psychological Dependence***—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

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

Literature revised June 28, 2007

PV 5904 AMP *PRINTED IN USA*

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

www.Cymbalta.com

Cymbalta® (duloxetine hydrochloride) Delayed-release Capsules PV 5904 AMP

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press

Volume 13 — CNS SPECTRUMS® — Number 1

The International Journal of Neuropsychiatric Medicine

COMMUNIQUES

CLINICAL UPDATES IN NEUROPSYCHIATRY

PEARLS IN CLINICAL NEUROSCIENCE

BRAIN REGIONS OF INTEREST

CONTINUING MEDICAL EDUCATION

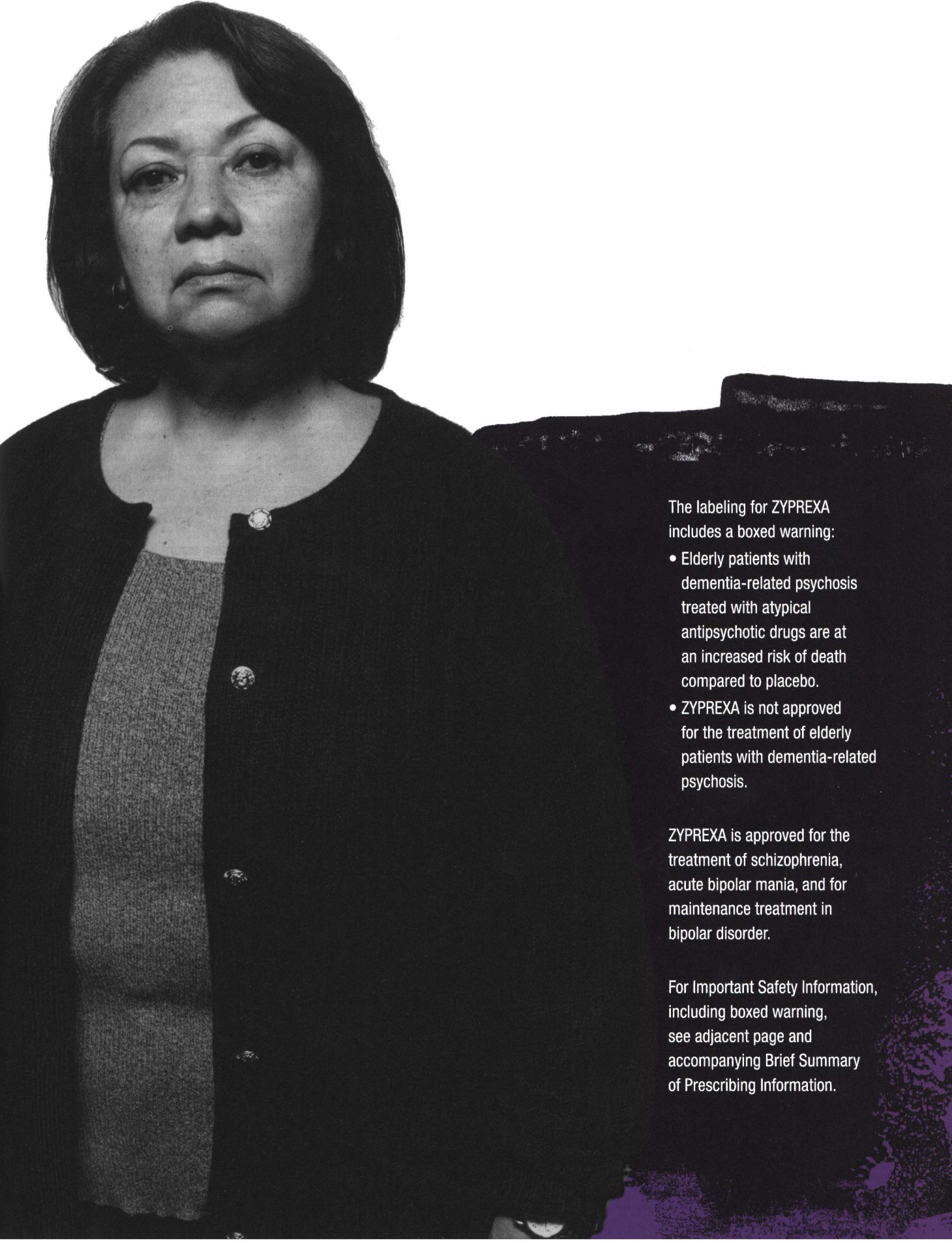
EXPERT ROUNDTABLE SUPPLEMENT

Founded in 1996, *CNS Spectrums* is indexed in the *Index Medicus* database and is available on MEDLINE under the citation *CNS Spectr*. *CNS Spectrums* is also the largest, peer-reviewed, indexed neuropsychiatric journal in the United States.

For editorial inquiries, please fax us at 212-328-0600 or e-mail José Ralat at jrr@mblcommunications.com. For bulk reprint purchases, please contact Christopher Naccari at cdn@mblcommunications.com.

This month's issue of *CNS Spectrums*, as well as a host of educational resources, enduring materials, and archived issues, is available at **www.cnsspectrums.com**.

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press



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

For Important Safety Information, including boxed warning, see adjacent page and accompanying Brief Summary of Prescribing Information.

Lilly

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press

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 patients in trials of ZYPREXA in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of CVAE in patients treated with ZYPREXA compared to patients treated with placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia—Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including olanzapine. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level. Patients taking olanzapine should be monitored regularly for worsening of glucose control. Persons with risk factors for diabetes who are starting on atypical antipsychotics should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Hyperlipidemia—Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised. Significant, and sometimes very high, elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Weight gain—Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight.

Neuroleptic malignant syndrome (NMS)—As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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

Other potentially serious adverse events include orthostatic hypotension, seizures, hyperprolactinemia, transaminase elevations, and dysphagia.

The safety and efficacy of ZYPREXA have not been established in patients under the age of 18 years.

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 event associated with ZYPREXA (vs placebo) in 6-week acute-phase schizophrenia trials was somnolence (26% vs 15%). Other common events were 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 event associated with ZYPREXA (vs placebo) in 3- and 4-week bipolar mania trials was somnolence (35% vs 13%). Other common events were 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%).

For complete safety profile, see the full Prescribing Information.

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press

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 (e.g., heart failure, sudden death) or infectious (e.g., 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 (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia—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. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. See the package insert for information on glycemic changes in adult and adolescent populations.

Physicians should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus or having borderline increased blood glucose level (fasting 100-126 mg/dL, non-fasting 140-200 mg/dL). Patients taking olanzapine 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.*

Hyperlipidemia—Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using olanzapine, is advised. Significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use. See the package insert for information on lipid changes in adult and adolescent populations.

Weight Gain—Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight. See the package insert for information on weight change in adult and adolescent populations.

Neuroleptic Malignant Syndrome (NMS)—Potentially fatal NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. See the package insert 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 D_2 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—Patients should be advised of the potential risk of hyperglycemia-related adverse events and monitored regularly for worsening of glucose control. Patients should be counseled that olanzapine is associated with weight gain and should have their weight monitored regularly. See the package insert for additional 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 Cmax and AUC of oral olanzapine by about 60%. Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine. Carbamazepine (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance. Neither ethanol (45 mg/70 kg single dose) nor warfarin (20 mg single dose) had an effect on olanzapine pharmacokinetics. Fluoxetine at 60 mg (single or multiple doses) causes a small increase in the Cmax of olanzapine and a small decrease in olanzapine clearance; however, the impact of this factor is small in comparison to the overall variability between individuals, and dose modification is not routinely recommended. *Fluvoxamine decreases the clearance of olanzapine; lower doses of olanzapine should be considered in patients* receiving fluvoxamine concomitantly. In vitro data suggest that a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility—*The incidence of liver hemangiomas and* hemangiosarcomas in female mice was significantly increased in one carcinogenicity study at 2 times the maximum human daily oral dose (MHDOD) but not in another study at 2-5 times the MHDOD (mg/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.

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—The safety and efficacy of olanzapine have not been established in patients under the age of 18 years. In premarketing clinical trials in patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger adult 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 package insert 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

ZYPREXA® (Olanzapine Tablets)
ZYPREXA® ZYDIS® (Olanzapine Orally Disintegrating Tablets)
ZYPREXA® IntraMuscular (Olanzapine for Injection) PV 5199 AMP

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

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

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

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.

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 (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

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

Literature revised October 1, 2007

PV 5199 AMP PRINTED IN USA

Eli Lilly and Company
Indianapolis, IN 46285, USA

www.ZYPREXA.com

https://doi.org/10.1017/S1092852900016060 Published online by Cambridge University Press