January 2005 Volume 10 — Number 1

CNS SPECTRUMS®

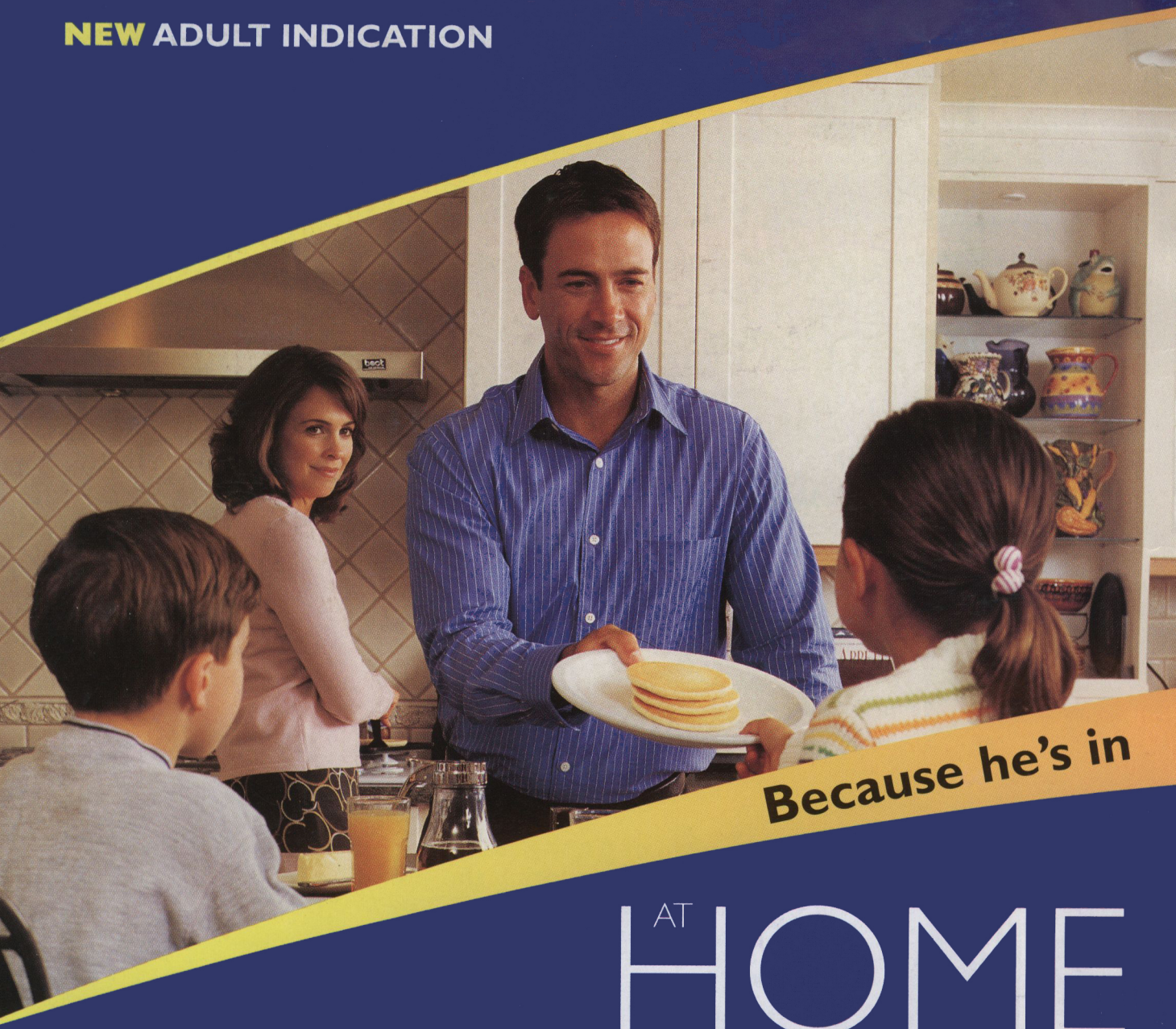
The International Journal of Neuropsychiatric Medicine

Index Medicus/MEDLINE citation: *CNS Spectr*

CME 3 Mount Sinai

https://doi.org/10.1017/S1092852900009810 Published online by Cambridge University Press

NEW ADULT INDICATION



Because he's in

AT HOME

Aim Higher With ADDERALL XR® —

The most common adverse events in pediatric trials included loss of appetite, insomnia, abdominal pain, and emotional lability. The most common adverse events in the adult trial included dry mouth, loss of appetite, insomnia, headache, and weight loss.

The effectiveness of ADDERALL XR for long-term use has not been systematically evaluated in controlled trials. As with other psychostimulants indicated for ADHD, there is a potential for exacerbating motor and phonic tics and Tourette's syndrome. A side effect seen with the amphetamine class is psychosis. Caution also should be exercised in patients with a history of psychosis.

Abuse of amphetamines may lead to dependence. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events. ADDERALL XR generally should not be used in children or adults with structural cardiac abnormalities. ADDERALL XR is contraindicated in patients with symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism and glaucoma, known hypersensitivity to this class of compounds, agitated states, history of drug abuse, or current or recent use of MAO inhibitors. ADDERALL XR should be prescribed with close physician supervision.

Reference: 1. Data on file, Shire US Inc., 2002.

www.ADDERALLXR.com
www.ADHDSupportCompany.com

Please see brief summary of prescribing information on adjacent page.

https://doi.org/10.1017/S1092852900009810 Published online by Cambridge University Press

demand all day long...

AT WORK

For Efficacy That Measures Up to Life's Demands

- Once-daily dosing provides all-day symptom control[1]
- Mean ADHD-RS total scores for adults receiving **ADDERALL XR** decreased by 41%[1]
- **ADDERALL XR** is the only stimulant medication approved to treat adults with ADHD[1]
- Clinical data in adults demonstrate that **ADDERALL XR** is generally well tolerated[1]

ONE DOSE DAILY

ADDERALL XR® CII

5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg CAPSULES

(Mixed Salts of a Single-Entity Amphetamine Product)

Dextroamphetamine Sulfate Dextroamphetamine Saccharate
Amphetamine Aspartate Monohydrate Amphetamine Sulfate

Reach new heights

Shire US Inc.
...your ADHD support company™
1-800-828-2088

Shire

https://doi.org/10.1017/S1092852900009810 Published online by Cambridge University Press

References: 1. Ambrosini PJ, Lopez FA, Chandler MC, et al. Safety and efficacy of ADDERALL XR in pediatric ADHD: results of an open-label community assessment trial. Poster presented at: 14th Annual CHADD International Conference; October 17, 2002; Miami Beach, Fla. **2.** Spencer T, Biederman J, Wilens T, et al. Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *J Am Acad Child Adolesc Psychiatry*. 1996;35:409-432. **3.** Lopez FA, Ambrosini PJ, Chandler MC, et al. ADDERALL XR in pediatric ADHD: quality of life measures from an open-label community assessment trial. Poster presented at: 14th Annual CHADD International Conference; October 17, 2002; Miami Beach, Fla. **4.** Lopez FA, Chandler MC, Biederman J, et al. Long-term Adderall XR treatment improves quality of life in ADHD children. Poster presented at: 156th Annual Meeting of the American Psychiatric Association; May 21, 2003; San Francisco, Calif.

BRIEF SUMMARY: Consult the full prescribing information for complete product information.

ADDERALL XR® CAPSULES **CII Rx Only**

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.

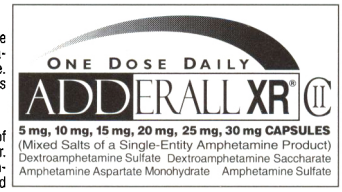
INDICATIONS

ADDERALL XR® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

The efficacy of ADDERALL XR® in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, and one controlled trial in adults who met DSM-IV criteria for ADHD (see CLINICAL PHARMACOLOGY), along with extrapolation from the known efficacy of ADDERALL®, the immediate-release formulation of this substance.

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

Psychosis: Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

Long-Term Suppression of Growth: Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally associated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR® generally should not be used in children or adults with structural cardiac abnormalities.

PRECAUTIONS

General: The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to *minimize the possibility of overdosage.*

Hypertension: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension (see CONTRAINDICATIONS). Blood pressure and pulse should be monitored at appropriate intervals in patients taking ADDERALL XR®, especially patients with hypertension.

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.

Drug Interactions: *Acidifying agents*—Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, etc.) lower absorption of amphetamines. *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. *Alkalinizing agents*—Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Co-administration of ADDERALL XR® and gastrointestinal alkalinizing agents, such as antacids, should be avoided. Urinary alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of 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: 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. These doses are approximately 2.4, 1.5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m² body surface area basis.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to l- ratio of 3:1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test *in vitro*. d,l-Amphetamine (1:1 enantiomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test, an equivocal response in the Ames test, and negative responses in the *in vitro* sister chromatid exchange and chromosomal aberration assays.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release) (d- to l- 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 (approximately 5 times the maximum recommended human dose of 30 mg/day on a mg/m² body surface area basis).

Pregnancy: *Pregnancy Category C. Amphetamine, in the enantiomer ratio present in ADDERALL® (d- to l- 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. These doses are approximately 1.5 and 8 times, respectively, the maximum recommended human dose of 30 mg/day [child] on a mg/m² body surface area basis. Fetal malformations and death have been reported in mice following parenteral administration of d-amphetamine doses of 50 mg/kg/day (approximately 6 times that of a human dose of 30 mg/day [child] on a mg/m² basis) 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 amphetamines 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: ADDERALL XR® is indicated for use in children 6 years of age and older.

Use in Children Under Six Years of Age: Effects of ADDERALL XR® in 3-5 year olds have not been studied. 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: ADDERALL XR® has not been studied in the geriatric population.

ADVERSE EVENTS

The premarketing development program for ADDERALL XR® included exposures in a total of 965 participants in clinical trials (635 pediatric patients, 248 adult patients, 82 healthy adult subjects). Of these, 635 patients (ages 6 to 12) were evaluated in two controlled clinical studies, one open-label clinical study, and two single-dose clinical pharmacology studies (N=40). Safety data on all patients are included in the discussion that follows. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

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

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

Adverse events associated with discontinuation of treatment: In two placebo-controlled studies of up to 5 weeks duration among children with ADHD, 2.4% (10/425) of ADDERALL XR® treated patients discontinued due to adverse events (including 3 patients with loss of appetite, one of whom also reported insomnia) compared to 2.7% (7/259) receiving placebo. The most frequent adverse events associated with discontinuation of ADDERALL XR® in controlled and uncontrolled, multiple-dose clinical trials of pediatric patients (N=595) are presented below. Over half of these patients were exposed to ADDERALL XR® for 12 months or more.

Adverse event	% of pediatric patients discontinuing (n=595)
Anorexia (loss of appetite)	2.9
Insomnia	1.5
Weight loss	1.2
Emotional lability	1.0
Depression	0.7

In one placebo-controlled 4-week study among adults with ADHD, patients who discontinued treatment due to adverse events among ADDERALL XR®-treated patients (N=191) were 3.1% (n=6) for nervousness including anxiety and irritability, 2.6% (n=5) for insomnia, 1% (n=2) each for headache, palpitation, and somnolence; and, 0.5% (n=1) each for ALT increase, agitation, chest pain, cocaine craving, elevated blood pressure, and weight loss.

Adverse events occurring in a controlled trial: Adverse events reported in a 3-week clinical trial of pediatric patients and a 4-week clinical trial in adults treated with ADDERALL XR® or placebo are presented in the tables 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.

Table 1 Adverse Events Reported by More Than 1% of Pediatric Patients Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 584 Patient Clinical Study

Body System	Preferred Term	ADDERALL XR® (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatigue)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Digestive System	Loss of Appetite	22%	2%
	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Liability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%
Metabolic/Nutritional	Weight Loss	4%	0%

Table 2 Adverse Events Reported by 5% or More of Adults Receiving ADDERALL XR® with Higher Incidence Than on Placebo in a 255 Patient Clinical Forced Weekly-Dose Titration Study*

Body System	Preferred Term	ADDERALL XR® (n=191)	Placebo (n=64)
General	Asthenia	6%	5%
	Headache	26%	13%
Digestive System	Loss of Appetite	33%	3%
	Diarrhea	6%	0%
	Dry Mouth	35%	5%
	Nausea	8%	3%
Nervous System	Agitation	8%	5%
	Anxiety	8%	5%
	Dizziness	7%	0%
	Insomnia	27%	13%
Cardiovascular System	Tachycardia	6%	3%
Metabolic/Nutritional	Weight Loss	11%	0%
Urogenital System	Urinary Tract Infection	5%	0%

Note: The following events did not meet the criterion for inclusion in Table 2 but were reported by 2% to 4% of adult patients receiving ADDERALL XR® with a higher incidence than patients receiving placebo in this study: infection, photosensitivity reaction, constipation, tooth disorder, emotional lability, libido decreased, somnolence, speech disorder, palpitation, twitching, dyspnea, sweating, dysmenorrhea, and impotence.

*included doses up to 60 mg.

The following adverse reactions have been associated with amphetamine use: 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, insomnia, 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, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects. Allergic: Urticaria. Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

ADDERALL XR® is 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 many times that 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.

OVERDOSAGE

Individual patient 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 mixed amphetamine salts from ADDERALL XR® should be considered when treating patients with overdose. Dispense in a tight, light-resistant container as defined in the USP. Store at 25° C (77° F). Excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature].

Manufactured for: **Shire US Inc.**, Newport, KY 41071 Made in USA For more information call 1-800-828-2088, or visit www.adderallxr.com. ADDERALL® and ADDERALL XR® are registered in the US Patent and Trademark Office.

403980 381 0107 004 Rev. 9/04

Shire

January 2005 Volume 10 – Number 1

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

https://doi.org/10.1017/S1092852900009810 Published online by Cambridge University Press

I never thought I could be myself again

Now I can

SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder and the treatment of schizophrenia. Patients should be periodically reassessed to determine the need for continued treatment.

Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension. A rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported with this class of medications, including SEROQUEL.

There have been reports of diabetes mellitus and hyperglycemia-related adverse events associated with the use of atypical antipsychotics, including SEROQUEL.

The most commonly observed adverse events associated with the use of SEROQUEL in clinical trials were somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, SGPT increase, dyspepsia, and weight gain.

Seroquel®
quetiapine fumarate
25 mg, 100 mg, 200 mg & 300 mg tablets

AstraZeneca
AstraZeneca Pharmaceuticals LP

Redefine Success

To prevent medication errors, write *"SEROQUEL"* clearly on your Rx pad. Spell *"SEROQUEL"* clearly over the phone.

www.SEROQUEL.com

Please see Brief Summary of Prescribing Information on following page.

221563 8/04

https://doi.org/10.1017/S1092852900009810 Published online by Cambridge University Press

CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

Table of Contents

Departments/Monthly Columns

Founded in 1996, ***CNS Spectrums*** is an *Index Medicus* journal and is available on MEDLINE under the citation *CNS Spectr.* It is available online at www.cnsspectrums.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 $140; foreign $195; in-training $85. For subscriptions: Phone: 212-328-0800; Fax: 212-328-0600; Web: www.cnsspectrums.com.

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

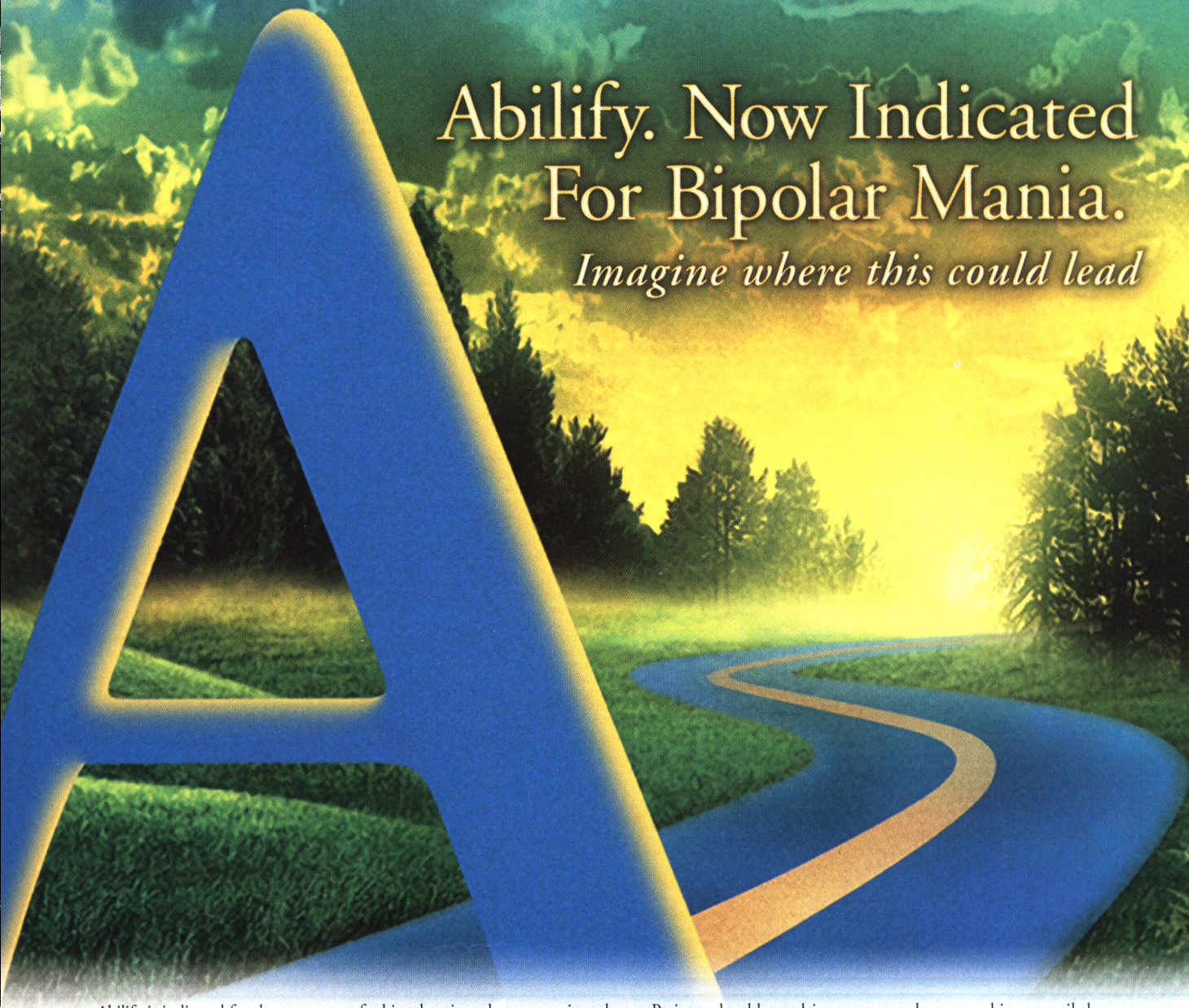
For editorial inquiries, please fax us at 212-328-0600 or e-mail us at jrr@mblcommunications.com. For bulk reprint purchases, please contact: Kathleen J. Skae at ks@mblcommunications.com.

BPA Worldwide Membership Applied for August 2004.

CNS SPECTRUMS **ONLINE**

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/S1092852900009810 Published online by Cambridge University Press



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

IMPORTANT SAFETY INFORMATION

As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia (TD).

Hyperglycemia, including some serious cases ranging from ketoacidosis to death, has been reported in patients treated with atypical antipsychotics. Abilify was not included in epidemiologic studies suggesting this risk; therefore the risk of hyperglycemia with Abilify is not known. However, there have been few reports of hyperglycemia in patients treated with Abilify. Patients should be appropriately tested before and monitored during treatment.

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

As with other antipsychotic drugs, Abilify should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold. Seizures occurred in 0.3% of bipolar patients treated with Abilify in placebo-controlled trials.

Patients should not drive or operate heavy machinery until they are certain Abilify does not affect them adversely.

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

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

The adverse events reported in a 26-week, double-blind schizophrenia trial comparing Abilify and placebo were generally consistent with those reported in the short-term, placebo-controlled schizophrenia trials, except for a higher incidence of tremor: 9% for Abilify vs 1% for placebo. In this study the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days), and were of limited duration (9/13 ≤10 days). Tremor infrequently led to discontinuation (<1%) of Abilify. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for Abilify was 4%.

Please see Brief Summary of full Prescribing Information on following pages.

Visit www.abilify.com for more information.

ABILIFY®
(aripiprazole)

Bristol-Myers Squibb Company Otsuka America Pharmaceutical, Inc.

https://doi.org/10.1017/S1092852900009810 Published online by Cambridge University Press

ABILIFY®

Rx only

(aripiprazole) Tablets

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

INDICATIONS AND USAGE

Schizophrenia

ABILIFY is indicated for the treatment of schizophrenia. The efficacy of ABILIFY in the treatment of schizophrenia was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY: Clinical Studies** in Full Prescribing Information). The efficacy of ABILIFY in maintaining stability in patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those other medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks was demonstrated in a placebo-controlled trial (see **CLINICAL PHARMACOLOGY: Clinical Studies**). The physician who elects to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION** in Full Prescribing Information).

Bipolar Mania

ABILIFY is indicated for the treatment of acute manic and mixed episodes associated with Bipolar Disorder. The efficacy of ABILIFY was established in two placebo-controlled trials (3-week) of inpatients with DSM-IV criteria for Bipolar I Disorder who were experiencing an acute manic or mixed episode with or without psychotic features (see **CLINICAL PHARMACOLOGY**). However, the effectiveness of ABILIFY for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been established in controlled clinical trials. Therefore, physicians who elect to use ABILIFY for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

ABILIFY is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole treatment in the premarketing worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, ABILIFY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with ABILIFY. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include ABILIFY suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of orthostatic hypotension associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on ABILIFY included: orthostatic hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%, aripiprazole 0.5%), and syncope (placebo 0.9%, aripiprazole 0.5%). The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo (in schizophrenia: 14% among aripiprazole-treated patients and 12% among placebo-treated patients and in bipolar mania: 3% among aripiprazole-treated patients and 2% among placebo-treated patients). Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizure

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients with schizophrenia in short-term, placebo-controlled trials. In short-term, placebo-controlled clinical trials of patients with bipolar mania, 0.3% (2/597) of aripiprazole-treated patients and 0.2% (1/436) placebo-treated patients experienced seizures. As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment

In short-term, placebo-controlled trials of schizophrenia, somnolence was reported in 11% of patients on ABILIFY compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% (1/926) of patients with schizophrenia on ABILIFY in short-term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar mania, somnolence was reported in 14% of patients on ABILIFY compared to 7% of patients on placebo, but did not lead to discontinuation of any patients with bipolar mania. Despite the relatively modest increased incidence of somnolence compared to placebo, ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **PRECAUTIONS**: *Use in Patients with Concomitant Illness*).

Suicide

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

Use in Patients with Concomitant Illness

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease: In a flexible dose (2 to 15 mg/day), 10-week, placebo-controlled study of aripiprazole in elderly patients (mean age: 81.5 years; range: 56 to 95 years) with psychosis associated with Alzheimer's dementia, 4 of 105 patients (3.8%) who received ABILIFY died compared to no deaths among 102 patients who received placebo during or within 30 days after termination of the double-blind portion of the study. Three of the patients (age 92, 91, and 87 years) died following the discontinuation of ABILIFY in the double-blind phase of the study (causes of death were pneumonia, heart failure, and shock). The fourth patient (age 78 years) died following hip surgery while in the double-blind portion of the study. The treatment-emergent adverse events that were reported at an incidence of ≥5% and having a greater incidence than placebo in this study were accidental injury, somnolence, and bronchitis. Eight percent of the ABILIFY-treated patients reported somnolence compared to one percent of placebo patients. In a small pilot, open-label, ascending-dose, cohort study (n=30) in elderly patients with dementia, ABILIFY was associated in a dose-related fashion with somnolence. The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration. Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses (see **CLINICAL PHARMACOLOGY: Special Populations:** *Renal Impairment* and *Hepatic Impairment* in Full Prescribing Information) is limited. ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

Information for Patients: Physicians are advised to consult full prescribing information to review issues to be discussed with patients for whom they prescribe ABILIFY.

Drug-Drug Interactions: Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally acting drugs and alcohol. Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents. *Potential for Other Drugs to Affect ABILIFY:* Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely. Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (e.g., carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels. *Ketoconazole:* Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased. *Quinidine:* Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when concomitant administration of quinidine with aripiprazole occurs. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased. *Carbamazepine:* Coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, aripiprazole dose should then be reduced. No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions** in Full Prescribing Information). *Potential for ABILIFY to Affect Other Drugs:* Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**). *Alcohol:* There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

Carcinogenesis, Mutagenesis, Impairment of Fertility: (Please See Full Prescribing Information).

Pregnancy

Pregnancy Category C

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits. Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg, however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity. Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of skeletal abnormality (fused sternebrae at 30 and 100 mg/kg) and minor skeletal variations (100 mg/kg). In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose. There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

Of the 7951 patients treated with aripiprazole in premarketing clinical trials, 991 (12%) were ≥65 years old and 789 (10%) were ≥75 years old. The majority (88%) of the 991 patients were diagnosed with dementia of the Alzheimer's type. Placebo-controlled studies of aripiprazole in schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects (≥65 years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients. Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia (see **PRECAUTIONS:** *Use in Patients with Concomitant Illness*). The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 7951 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5235 patient-years of exposure. A total of 2280 aripiprazole-treated patients were treated for at least 180 days and 1558 aripiprazole-treated patients had at least 1 year of exposure. The conditions and duration of treatment with aripiprazole included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure. Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; i.e., all reported events are included. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

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

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

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

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

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

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

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

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

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

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

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

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

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

Treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset were: *Body as a Whole*—headache, asthenia, accidental injury, peripheral edema; *Cardiovascular System*—hypertension; *Digestive System*—nausea, dyspepsia, vomiting, constipation; *Musculoskeletal System*—myalgia; *Nervous System*—agitation, anxiety, insomnia, somnolence, akathisia, lightheadedness, extrapyramidal syndrome, tremor, increased salivation; *Respiratory System*—pharyngitis, rhinitis, coughing; *Special Senses*—blurred vision. An examination of population subgroups did not reveal any clear evidence of differential adverse event incidence on the basis of age, gender, or race.

Dose-Related Adverse Events

Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in patients with schizophrenia comparing various fixed doses (2, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 17% vs. 12% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the bipolar mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups. Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

Laboratory Test Abnormalities

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

Weight Gain

In 4- to 6-week trials in schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively), and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)]. In 3-week trials in mania, the mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. -0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (3%) compared to placebo (2%). Table 2 provides the weight change results from a long-term (26-week), placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 2: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample

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

Table 3 provides the weight change results from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

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

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

ECG Changes

Between group comparisons for pooled, placebo-controlled trials in patients with schizophrenia, revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters; in fact, within the dose range of 10 to 30 mg/day, aripiprazole tended to slightly shorten the QT_c interval. Aripiprazole was associated with a median increase in heart rate of 4 beats per minute compared to a 1 beat per minute increase among placebo patients.

Additional Findings Observed in Clinical Trials

Adverse Events in a Long-Term, Double-Blind, Placebo-Controlled Trial

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

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 7951 patients. All reported events are included except those already listed in other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. *Body as a Whole: Frequent* – flu syndrome, fever, chest pain, rigidity (including neck and extremity), neck pain, pelvic pain; *Infrequent* – face edema, suicide attempt, malaise, migraine, chills, photosensitivity, tightness (including abdomen, back, extremity, head, jaw, neck, and tongue), jaw pain, bloating, enlarged abdomen, chest tightness, throat pain; *Rare* – moniliasis, head heaviness, throat tightness, Mendelson's syndrome, heat stroke. *Cardiovascular System: Frequent* – tachycardia (including ventricular and supraventricular), hypotension, bradycardia; *Infrequent* – palpitation, hemorrhage, heart failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris, pallor, cardiopulmonary arrest, phlebitis; *Rare* – bundle branch block, atrial flutter, vasovagal reaction, cardiomegaly, thrombophlebitis, cardiopulmonary failure. *Digestive System: Frequent* – nausea and vomiting; *Infrequent* – increased appetite, dysphagia, gastroenteritis, flatulence, tooth caries, gastritis, gingivitis, gastrointestinal hemorrhage, hemorrhoids, gastroesophageal reflux, periodontal abscess, fecal incontinence, rectal hemorrhage, stomatitis, colitis, tongue edema, cholecystitis, mouth ulcer, oral moniliasis, eructation, fecal impaction, cholelithiasis; *Rare* – esophagitis, hematemesis, intestinal obstruction, gum hemorrhage, hepatitis, peptic ulcer, glossitis, metena, duodenal ulcer, cheilitis, hepatomegaly, pancreatitis. *Endocrine System: Infrequent* – hypothyroidism; *Rare* – goiter, hyperthyroidism. *Hemic/Lymphatic System: Frequent* – ecchymosis, anemia; *Infrequent* – hypochromic anemia, leukocytosis, leukopenia (including neutropenia), lymphadenopathy, eosinophilia, macrocytic anemia; *Rare* – thrombocythemia, thrombocytopenia, petechiae. *Metabolic and Nutritional Disorders: Frequent* – weight loss, creatine phosphokinase increased, dehydration; *Infrequent* – edema, hyperglycemia, hypercholesteremia, hypokalemia, diabetes mellitus, hypoglycemia, hyperlipemia, SGPT increased, thirst, BUN increased, hyponatremia, SGOT increased, creatinine increased, cyanosis, alkaline phosphatase increased, bilirubinemia, iron deficiency anemia, hyperkalemia, hyperuricemia, obesity; *Rare* – lactic dehydrogenase increased, hypernatremia, gout, hypoglycemic reaction. *Musculoskeletal System: Frequent* – muscle cramp; *Infrequent* – arthralgia, myasthenia, arthrosis, bone pain, arthritis, muscle weakness, spasm, bursitis, myopathy; *Rare* – rheumatoid arthritis, rhabdomyolysis, tendonitis, tenosynovitis. *Nervous System: Frequent* – depression, nervousness, schizophrenic reaction, hallucination, hostility, confusion, paranoid reaction, suicidal thought, abnormal gait, manic reaction, delusions, abnormal dream; *Infrequent* – emotional lability, twitch, cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence, extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, panic attack, decreased libido, hypersomnia, dyskinesia, manic depressive reaction, ataxia, visual hallucination, cerebrovascular accident, hypokinesia, depersonalization, impaired memory, delirium, dysarthria, tardive dyskinesia, amnesia, hyperactivity, increased libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia, increased reflexes, akinesia, decreased consciousness, hyperesthesia, slowed thinking; *Rare* – blunted affect, euphoria, incoordination, oculogyric crisis, obsessive thought, hypotonia, buccoglossal syndrome, decreased reflexes, derealization, intracranial hemorrhage. *Respiratory System: Frequent* – sinusitis, dyspnea, pneumonia, asthma; *Infrequent* – epistaxis, hiccup, laryngitis, aspiration pneumonia; *Rare* – pulmonary edema, increased sputum, pulmonary embolism, hypoxia, respiratory failure, apnea, dry nasal passages, hemoptysis. *Skin and Appendages: Frequent* – skin ulcer, sweating, dry skin; *Infrequent* – pruritus, vesiculobullous rash, acne, eczema, skin discoloration, alopecia, seborrhea, psoriasis; *Rare* – maculopapular rash, exfoliative dermatitis, urticaria. *Special Senses: Frequent* – conjunctivitis; *Infrequent* – ear pain, dry eye, eye pain, tinnitus, cataract, otitis media, altered taste, blepharitis, eye hemorrhage, deafness; *Rare* – diplopia, frequent blinking, ptosis, otitis externa, amblyopia, photophobia. *Urogenital System: Frequent* – urinary incontinence; *Infrequent* – urinary frequency, leukorrhea, urinary retention, cystitis, hematuria, dysuria, amenorrhea, vaginal hemorrhage, abnormal ejaculation, kidney failure, vaginal moniliasis, urinary urgency, gynecomastia, kidney calculus, albuminuria, breast pain, urinary burning; *Rare* – nocturia, polyuria, menorrhagia, anorgasmy, glycosuria, cervicitis, uterus hemorrhage, female lactation, urolithiasis, priapism.

Other Events Observed During the Postmarketing Evaluation of Aripiprazole

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

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILIFY is not a controlled substance.

Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Management of Overdosage

No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and, if QT_c interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%.

Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

Storage

Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature].

Marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA
and Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

Distributed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

U.S. Patent Nos. 4,734,416 and 5,006,528

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

Otsuka America Pharmaceutical, Inc.
Rockville, MD 20850 U.S.A.

D6-B0001A-09-04 AP4749/10-04
1156731A8
Revised September 2004