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CNS SPECTRUMS®

The International Journal of Neuropsychiatric Medicine

4

Pediatric Psychopharmacology

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GUIDE TO *DSM-IV* AND *ICD-10* CODES

	DSM-IV	*ICD-10*
Dementia of the Alzheimer's Type, With Early Onset With Depressed Mood		
Specify if: With Behavioral Disturbance	290.13	F00.03
Dementia of the Alzheimer's Type, With Late Onset With Depressed Mood		
Specify if: With Behavioral Disturbance	290.21	F00.13
Delirium Due to: Indicate General Medical Condition	293.0	F05.0
Psychotic Disorder Due to: Indicate General Medical Condition With Delusions	293.81	F06.2
With Hallucinations	293.82	F06.0
Mood Disorder Due to: Indicate General Medical Condition	293.83	F06
Anxiety Disorder Due to: Indicate General Medical Condition	293.89	F06.4
Amnestic Disorder Due to: Indicate General Medical Condition	294.0	F02.8
Dementia NOS	294.8	F03
Amnestic Disorder NOS	294.8	R41.3
Schizophrenia	295	F20
Schizophrenia—Disorganized Type	295.10	F20.1
Schizophrenia—Catatonic Type	295.20	F20.2
Schizophrenia—Paranoid Type	295.30	F20.0
Schizophrenia—Residual Type	295.60	F20.5
Schizoaffective Disorder	295.70	F25
Schizophrenia—Undifferentiated Type	295.90	F20.3
Major Depressive Disorder	296	F32
Bipolar I Disorder	296	F30
Bipolar Disorder NOS	296.80	F39
Bipolar II Disorder	296.89	F31.8
Mood Disorder NOS	296.90	F39
Psychotic Disorder NOS	298.9	F29
Autistic Disorder	299.00	F84
Asperger's Disorder	299.80	F84.5
Pervasive Developmental Disorder NOS	299.80	F84.9
Anxiety Disorder NOS	300.00	F41.9
Panic Disorder Without Agoraphobia	300.01	F41
Generalized Anxiety Disorder	300.02	F41.1
Dissociative Identity Disorder	300.14	F44.81
Dissociative Disorder NOS	300.15	F44.9
Factitious Disorder NOS	300.19	F68.1
Panic Disorder With Agoraphobia	300.21	F40.01
Agoraphobia Without History of Panic Disorder	300.22	F40
Social Phobia	300.23	F40.1
Specific Phobia	300.29	F40.2
Obsessive-Compulsive Disorder	300.3	F42.8
Dysthymic Disorder	300.4	F34.1
Depersonalization Disorder	300.6	F48.1
Body Dysmorphic Disorder	300.7	F45.2
Somatization Disorder	300.81	F45.
Somatoform Disorder NOS	300.81	F45.9
Cyclothymic Disorder	301.13	F34
Alcohol Dependence	303.90	F10.2
Cocaine Dependence	304.20	F14.2
Cannabis Dependence	304.30	F12.2
Amphetamine Dependence	304.40	F15.2
Alcohol Abuse	305.00	F10.1
Cannabis Abuse	305.20	F12.1
Cocaine Abuse	305.60	F14.1
Amphetamine Abuse	305.70	F15.1
Stuttering	307.0	F98.5
Anorexia Nervosa	307.1	F50
Tic Disorder NOS	307.20	F95.9
Tourette Disorder	307.23	F95.2
Primary Insomnia	307.42	F51.0
Primary Hypersomnia	307.44	F51.1
Sleepwalking Disorder	307.46	F51.3
Dyssomnia NOS	307.47	F51.9
Nightmare Disorder	307.47	F51.5
Parasomnia NOS	307.47	F51.8
Eating Disorder NOS	307.50	F50.9
Bulimia Nervosa	307.51	F50.2
Feeding Disorders of Infancy or Early Childhood	307.59	F98.2
Communication Disorder NOS	307.9	F80.9
Posttraumatic Stress Disorder	309.81	F43.1
Depressive Disorder NOS	311	F32.9
Impulse-Control Disorder NOS	312.30	F63.9
Pathological Gambling	312.31	F63.0
Pyromania	312.33	F63.1
Kleptomania	312.34	F63.2
Trichotillomania	312.39	F63.3
Disruptive Behavior Disorder NOS	312.9	F91.9
Attention-Deficit/Hyperactivity Disorder, Combined Type	314.01	F90
Attention-Deficit/Hyperactivity Disorder NOS	314.9	F90.9
Learning Disorder NOS	315.9	F81.9
Developmental Coordination Disorder	315.4	F82
Narcolepsy	347	G47.4
Sleep Disorder Due to: Indicate General Medical Condition	780	G47
Delirium NOS	780.09	F05.9

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Time for wakefulness

PROVIGIL® (modafinil) TABLETS
BRIEF SUMMARY: Consult Package Insert for Complete Prescribing Information
INDICATIONS and USAGE: To improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.
CONTRAINDICATIONS: Known hypersensitivity to PROVIGIL
PRECAUTIONS: ***General:*** Patients should be cautioned about operating an automobile or other hazardous machinery until they are reasonably certain that PROVIGIL therapy will not adversely affect their ability to engage in such activities.
Cardiovascular System: In clinical studies of PROVIGIL, signs and symptoms including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on ECG were observed in 3 subjects in association with mitral valve prolapse or left ventricular hypertrophy. It is recommended that PROVIGIL tablets not be used in patients with a history of left ventricular hypertrophy or ischemic ECG changes, chest pain, arrhythmia or other clinically significant manifestations of mitral valve prolapse in association with CNS stimulant use. Patients with a recent history of MI or unstable angina should be treated with caution. Periodic monitoring of hypertensive patients taking PROVIGIL may be appropriate.
Central Nervous System: Caution should be exercised when PROVIGIL is given to patients with a history of psychosis.
Patients with Severe Renal Impairment: Treatment with PROVIGIL resulted in much higher exposure to its inactive metabolite, modafinil acid, but not PROVIGIL itself.
Patients with Severe Hepatic Impairment: PROVIGIL should be administered at a reduced dose because its clearance is decreased.
Patients Using Contraceptives: The effectiveness of steroidal contraceptives may be reduced when used with PROVIGIL and for 1 month after discontinuation. Alternative or concomitant methods of contraception are recommended during and for 1 month after treatment.
Information for Patients: Physicians are advised to discuss the following with patients taking PROVIGIL:
Pregnancy: Animal studies to assess the effects of PROVIGIL on reproduction and the developing fetus were not conducted so as to ensure a comprehensive evaluation of the potential of PROVIGIL to adversely affect fertility, or cause embryolethality or teratogenicity. Patients should notify their physician if they become pregnant or intend to become pregnant during therapy. They should be cautioned of the potential increased risk of pregnancy when using steroidal contraceptives (including depot or implantable contraceptives) with PROVIGIL and for 1 month after discontinuation. ***Nursing:*** Patients should notify their physician if they are breast feeding. ***Concomitant Medication:*** Patients should inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, because of the potential for drug interactions. ***Alcohol:*** It is prudent to avoid alcohol while taking PROVIGIL. ***Allergic Reactions:*** Patients should notify their physician if they develop a rash, hives, or a related allergic phenomenon.
Drug Interactions: ***CNS Active Drugs:*** In a single-dose study, coadministration of PROVIGIL 200 mg with *methylphenidate* 40 mg delayed the absorption of PROVIGIL by approximately 1 hour. The coadministration of a single dose of *clomipramine* 50 mg with PROVIGIL 200 mg/day did not affect the pharmacokinetics of either drug. One incident of increased levels of *clomipramine* and its active metabolite desmethylclomipramine has been reported. In a single-dose study with PROVIGIL (50, 100 or 200 mg) and *triazolam* 0.25 mg, no clinically important alterations in the safety profile of either drug were noted. In the absence of interaction studies with *monoamine oxidase (MAO) inhibitors*, caution should be exercised.
Potential Interactions with Drugs That Inhibit, Induce, or Are Metabolized by Cytochrome P-450 Isoenzymes and Other Hepatic Enzymes: Chronic dosing of PROVIGIL 400 mg/day resulted in ~20% mean decrease in PROVIGIL plasma trough concentration suggesting that PROVIGIL may have caused induction of its metabolism. Coadministration of potent inducers of CYP3A4 (eg, carbamazepine, phenobarbital, rifampin) or inhibitors of CYP3A4 (eg, ketoconazole, itraconazole) could alter the levels of PROVIGIL. Caution needs to be exercised when PROVIGIL is coadministered with drugs that depend on hepatic enzymes for their clearance; some dosage adjustment may be required. Potentially relevant *in vivo* effects of PROVIGIL based on *in vitro* data are:
A slight induction of CYP1A2 and CYP2B6 in a concentration-dependent manner has been observed.
A modest induction of CYP3A4 in a concentration-dependent manner may result in lower levels of CYP3A4 substrates (eg, cyclosporine, steroidal contraceptives, theophylline).
An apparent concentration-related suppression of expression of CYP2C9 activity may result in higher levels of CYP2C9 substrates (eg, warfarin, phenytoin).
A reversible inhibition of CYP2C19 may result in higher levels of CYP2C19 substrates (eg, diazepam, propranolol, phenytoin, S-mephenytoin).
In some patients deficient in CYP2D6, the amount of metabolism via CYP2C19 may be substantially larger. Co-therapy with PROVIGIL may increase levels of some tricyclic antidepressants (eg, clomipramine, desipramine).
Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis: The highest dose studied in carcinogenesis studies represents 1.5 times (mouse) or 3 times (rat) the maximum recommended human daily dose of 200 mg on a mg/m^2 basis. There was no evidence of tumorigenesis associated with PROVIGIL administration in these studies, but because the mouse study used an inadequate high dose below that representative of a maximum tolerated dose, the carcinogenic potential in that species has not been fully evaluated. ***Mutagenesis:*** There was no evidence of mutagenic or clastogenic potential of PROVIGIL. ***Impairment of Fertility:*** When PROVIGIL was administered orally to male and female rats prior to and throughout mating and gestation at up to 100 mg/kg/day (4.8 times the maximum recommended daily dose of 200 mg on a mg/m^2 basis) no effects on fertility were seen. This study did not use sufficiently high doses or large enough sample size to adequately assess effects on fertility.
Pregnancy: Pregnancy Category C: Embryotoxicity was observed in the absence of maternal toxicity when rats received oral PROVIGIL throughout the period of organogenesis. At 200 mg/kg/day (10 times the maximum recommended daily human dose of 200 mg on a mg/m^2 basis) there was an increase in resorption, hydronephrosis, and skeletal variations. The no-effect dose for these effects was 100 mg/kg/day (5 times the maximum recommended daily human dose on a mg/m^2 basis). When rabbits received oral PROVIGIL throughout organogenesis at doses up to 100 mg/kg/day (10 times the maximum recommended daily human dose on a mg/m^2 basis), no embryotoxicity was seen. Neither of these studies, however, used optimal doses for the evaluation of embryotoxicity. Although a threshold dose for embryotoxicity has been identified, the full spectrum of potential toxic effects on the fetus has not been characterized. When rats were dosed throughout gestation and lactation at doses up to 200 mg/kg/day, no developmental toxicity was noted post-natally in the offspring. There are no adequate and well-controlled trials with PROVIGIL in pregnant women. PROVIGIL should be used during pregnancy only if the potential benefit outweighs the potential risk.

PROVIGIL® (MODAFINIL)C Tablets

Labor and Delivery: The effect of PROVIGIL on labor and delivery in humans has not been systematically investigated. Seven normal births occurred in patients who had received PROVIGIL during pregnancy.
Nursing Mothers: It is not known whether PROVIGIL or its metabolite are excreted in human milk. Caution should be exercised when PROVIGIL is administered to a nursing woman.
PEDIATRIC USE: Safety and effectiveness in individuals below 16 years of age have not been established.
GERIATRIC USE: Safety and effectiveness in individuals above 65 years of age have not been established.
ADVERSE REACTIONS: PROVIGIL has been evaluated for safety in over 2200 subjects, of whom more than 900 subjects with narcolepsy or narcolepsy/hypersomnia were given at least 1 dose of PROVIGIL. In controlled clinical trials, PROVIGIL was well tolerated, and most adverse experiences were mild to moderate. The most commonly observed adverse events (≥5%) associated with the use of PROVIGIL more frequently than placebo-treated patients in controlled US and foreign studies were headache, infection, nausea, nervousness, anxiety, and insomnia. In US controlled trials, 5% of the 369 patients who received PROVIGIL discontinued due to an adverse experience. The most frequent (≥1%) reasons for discontinuation that occurred at a higher rate for PROVIGIL than placebo patients were headache (1%), nausea (1%), depression (1%) and nervousness (1%). The incidence of adverse experiences that occurred in narcolepsy patients at a rate of ≥1% and were more frequent in patients treated with PROVIGIL than in placebo patients in US controlled trials are listed below. Consult full prescribing information on adverse events.
Body as a whole: Headache,[1] chest pain, neck pain, chills, rigid neck, fever/chills
Digestive: Nausea,[1] diarrhea,[1] dry mouth,[1] anorexia,[1] abnormal liver function,[2] vomiting, mouth ulcer, gingivitis, thirst
Respiratory system: Rhinitis,[1] pharyngitis,[1] lung disorder, dyspnea, asthma, epistaxis
Nervous system: Nervousness,[1] dizziness, depression, anxiety, cataplexy, insomnia, paresthesia, dyskinesia,[3] hypertonia, confusion, amnesia, emotional lability, ataxia, tremor
Cardiovascular: Hypotension, hypertension, vasodilation, arrhythmia, syncope
Hemic/Lymphatic: Eosinophilia
Special senses: Amblyopia, abnormal vision
Metabolic/Nutritional: Hyperglycemia, albuminuria
Musculo-skeletal: Joint disorder
Skin/Appendages: Herpes simplex, dry skin
Urogenital: Abnormal urine, urinary retention, abnormal ejaculation[4]
[1]Incidence ≥5%, [2]Elevated liver enzymes, [3]Oro-facial dyskinesias, [4]Incidence adjusted for gender.
Dose Dependency: In US trials, the only adverse experience more frequent (≥5% difference) with PROVIGIL 400 mg/day than PROVIGIL 200 mg/day and placebo was headache.
Vital Signs Changes: There were no consistent effects or patterns of change in vital signs for patients treated with PROVIGIL in the US trials.
Weight Changes: There were no clinically significant differences in body weight change in patients treated with PROVIGIL compared to placebo.
Laboratory Changes: Mean plasma levels of gamma-glutamyl transferase (GGT) were higher following administration of PROVIGIL but not placebo. Few subjects (1%) had GGT elevations outside the normal range. Shift to higher, but not clinically significantly abnormal, GGT values appeared to increase with time on PROVIGIL. No differences were apparent in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total protein, albumin, or total bilirubin. There were more elevated eosinophil counts with PROVIGIL than placebo in US studies; the differences were not clinically significant.
ECG Changes: No treatment-emergent pattern of ECG abnormalities was found in US studies following administration of PROVIGIL.
Postmarketing Reports
In addition to the adverse events observed during clinical trials, the following adverse events have been identified during post-approval use of PROVIGIL in clinical practice. Because these adverse events are reported voluntarily from a population of uncertain size, reliable estimates of their frequency cannot be made.
Hematologic: Agranulocytosis
Central Nervous System: Symptoms of psychosis, symptoms of mania
DRUG ABUSE and DEPENDENCE: Abuse Potential and Dependence: In addition to wakefulness-promoting effect and increased locomotor activity in animals, in humans, PROVIGIL produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. *In vitro*, PROVIGIL binds to the dopamine reuptake site and causes an increase in extracellular dopamine but no increase in dopamine release. PROVIGIL is reinforcing, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine. In some studies PROVIGIL was also partially discriminated as stimulant-like. Physicians should follow patients closely, especially those with a history of drug and/or stimulant (eg, methylphenidate, amphetamine, or cocaine) abuse. Patients should be observed for signs of misuse or abuse (eg, incrementation of doses or drug-seeking behavior). In individuals experienced with drugs of abuse, PROVIGIL produced psychoactive and euphoric effects and feelings consistent with other scheduled CNS stimulants (methylphenidate). Patients should be observed for signs of misuse or abuse.
Withdrawal: Following 9 weeks of PROVIGIL use in 1 US trial, no specific symptoms of withdrawal were observed during 14 days of observation, although sleepiness returned in narcoleptic patients.
OVERDOSAGE: Human Experience: A total of 151 doses of ≥1000 mg/day (5 times the maximum recommended daily dose) have been recorded for 32 individuals. Doses of 4500 mg and 4000 mg were taken intentionally by 2 patients participating in foreign depression studies. In both cases, adverse experiences observed were limited, expected, and not life-threatening, and patients recovered fully by the following day. The adverse experiences included excitation or agitation, insomnia, and slight or moderate elevations in hemodynamic parameters. In neither of these cases nor in others with doses ≥1000 mg/day, including experience with up to 21 consecutive days of dosing at 1200 mg/day, were any unexpected effects or specific organ toxicities observed. Other observed high-dose effects in clinical studies have included anxiety, irritability, aggressiveness, confusion, nervousness, tremor, palpitations, sleep disturbances, nausea, diarrhea, and decreased prothrombin time. **Overdose Management:** No specific antidote to the toxic effects of PROVIGIL overdose has been identified. Overdoses should be managed with primarily supportive care, including cardiovascular monitoring. Emesis or gastric lavage should be considered. There are no data suggesting that dialysis or urinary acidification or alkalinization enhance drug elimination. The physician should consider contacting a poison-control center on the treatment of any overdose.
Manufactured for: **Cephalon, Inc.**, West Chester, PA 19380
For more information about PROVIGIL, please call Cephalon Professional Services at 1-800-896-5855 or visit our Website at **www.PROVIGIL.com.**

Cephalon

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The International Journal of Neuropsychiatric Medicine

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Editorial Advisory Board Questionnaire

Dear Dr. Nicolini:

Please take a minute to respond to the questions below regarding the future editorial content and direction of CNS Spectrums:

How would you rate the overall content of this issue?
Excellent____ Good_____ Satisfactory_____Unsatisfactory_____

Which articles were of most interest and why?

_____

_____

_____

Which articles were of least interest and why? How could this issue have been improved?

_____

_____

_____

Which columns do you find most interesting and why?
A. The Neurology of Behavior _____
B. Point & Commentary _____
C. CNS Reports™ _____

What are your opinions about the CME quiz section? Do you find it reflective of the material in the issue?

_____

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What areas of neurology, psychiatry and neuropsychiatry would you like to see represented in future issues?

_____

_____

_____

Please add any other comments or suggestions you may have regarding the editorial content and/or future issues of CNS Spectrums.

_____

_____

_____

Please fax this form to 212-328-0600,
Attn: Eileen S. Seligman, Assistant Acquisitions Editor

CONTACT: Christopher D. Naccari

Managing Editor

P: 212-328-0800 ext. 210

cdn@mblcommunications.com

For Immediate Release

MBL Communications, Inc. Announces the Publication of *Primary Psychiatry* in Poland as *Psychiatria po Dyplomie*

(**NEW YORK, NY** – March 31, 2003) — MBL Communications, Inc. announced today that it will begin publishing *Primary Psychiatry* in Poland in June of 2003 through an international licensing agreement with Medical Tribune Polska Sp. z. o. o. (MTP). The Polish title of *Primary Psychiatry* will be *Psychiatria po Dyplomie* (*PpD*).

MTP is a Warsaw-based, Polish medical journal publisher with experience in producing, publishing, and selling medical journals in Poland. MBL Communications, Inc. has granted MTP the exclusive rights to translate selected *Primary Psychiatry* reviews from English into Polish in *PpD*. The agreement allows MTP to publish *PpD* quarterly with two issues in 2003 and four issues in 2004.

MTP will appoint a leading Polish opinion leader as the editor-in-chief, and that editor-in-chief will then select which articles from *Primary Psychiatry* are to be translated. Each issue of *PpD* will feature a preface by a Polish opinion leader and each selected article will be prefaced by a short commentary from a different Polish opinion leader.

Primary Psychiatry—The Voice of Clinical Psychiatric Medicine, is the largest circulation, peer-reviewed psychiatric journal in the United States and it addresses the significant comorbid interface between psychiatry and primary care medicine.

- more -

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MBL Communications, Inc., an independent publisher of neuroscience journals based in New York, also publishes *CNS Spectrums*—The International Journal of Neuropsychiatric Medicine, and a host of enduring material programs in conjunction with Mount Sinai School of Medicine. *CNS Spectrums* is an *Index Medicus* journal designed to bridge the needs of practicing psychiatrists and neurologists. It is also indexed in EMBASE/Excerpta Medica, DIALOG, SilverPlatter, OVID, and Lexis-Nexis. *CNS Spectrums* is endorsed by, and is the official journal of, The International Neuropsychiatric Association, with members in 30 countries.

If you would like to learn more about *CNS Spectrums* or *Primary Psychiatry*, please visit MBL Communications, Inc. at: www.mblcommunications.com

Time for wakefulness

A unique wake-promoting agent

PROVIGIL promotes daytime wakefulness, improving patients' ability to participate in daily activities—with no effect on nighttime sleep.[1-3]

Long-term safety

The long-term safety profile of PROVIGIL has been demonstrated for up to 136 weeks.[4]

PROVIGIL was generally well tolerated. Most frequently reported adverse events in clinical trials were headache, nausea, nervousness, anxiety, infection, and insomnia. Most adverse events were mild to moderate. PROVIGIL may interact with drugs that inhibit, induce, or are metabolized by cytochrome P450 isoenzymes.

Dosing

Recommended dose for PROVIGIL is 200 mg taken orally once daily in the morning. Both PROVIGIL doses, 200 mg and 400 mg QD, were effective.

PROVIGIL is indicated to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy.

References: 1. PROVIGIL full prescribing information. **2.** US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol*. 1998;43:88-97. **3.** US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology*. 2000;54:1166-1175. **4.** Data on file, Cephalon, Inc.

PROVIGIL®
(MODAFINIL)C IV
Tablets

Wake up to life.™

Please see brief summary of prescribing information on adjacent page.
For more information, call 1-800-896-5855 or visit our Website at www.PROVIGIL.com.

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CNS Spectrums' *editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients, and original research and reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. The journal's goal is to serve as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of central nervous system disease, illness, or trauma.*

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ABILIFY™ Rx only

(aripiprazole) Tablets

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

INDICATIONS AND USAGE

ABILIFY (aripiprazole) 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**). The long-term efficacy of aripiprazole in the treatment of schizophrenia has not been established. 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.

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 irre*versible, 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 peri*ods 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.

PRECAUTIONS

General: *Orthostatic Hypotension:* Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY (aripiprazole) included: *orthostatic hypotension (placebo 1%, aripiprazole 1.9%); orthostatic lightheaded*ness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). 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 (14% among aripiprazole-treated patients and 12% 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 in short-term, placebo-controlled trials. 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, 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 on ABILIFY in short-term, placebo-controlled trials. 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 close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY 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 (aripiprazole) 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*) 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**). *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 Category C: 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 5592 patients treated with aripiprazole in premarketing clinical trials, 659 (12%) were ≥65 years old and 525 (9%) were ≥75 years old. The majority (91%) of the 659 patients were diagnosed with dementia of the Alzheimer's type. Placebo-controlled studies of aripiprazole in schizophrenia 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 5592 patients who participated in multiple-dose premarketing trials in schizophrenia, bipolar mania, and dementia *of the Alzheimer's type, and who had approximately 3639 patient-years of expo*sure. *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 Events Occurring at an Incidence of >2% 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) at an incidence of 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence was greater than the incidence reported for placebo were: *Body as a Whole*—headache, asthenia, and fever; *Digestive System*—nausea, vomiting, and constipation; *Nervous System*—anxiety, insomnia, lightheadedness, somnolence, akathisia, and tremor; *Respiratory System*—rhinitis and coughing; *Skin and Appendages*—rash; *Special Senses*—blurred vision. *Dose-Related Adverse Events:* 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 short-term, placebo-controlled trials, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. Objectively collected data from those trials on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) also did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). *Laboratory Test Abnormalities:* A between group comparison for 4- to 6-week placebo-controlled trials revealed no medically important differences between aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. *Weight Gain:* In short-term trials, 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%)]. *ECG Changes:* Between group comparisons for pooled placebo-controlled trials revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters; 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. *Other Adverse Events Observed During Clinical Trials:* Following is a list of modified COSTART terms that reflect treatment-emergent adverse events reported by patients treated with aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 5592 patients. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it. Frequent events occurred in at least 1/100 patients; infrequent events occurred in 1/100 to 1/1000 patients; rare events in fewer than 1/1000 patients. *Body as a Whole: Frequent* – flu syndrome, peripheral edema, chest pain, neck pain, neck rigidity; *Infrequent* – pelvic pain, suicide attempt, face edema, malaise, photosensitivity, arm rigidity, jaw pain, chills, bloating, jaw tightness, enlarged abdomen, chest tightness; *Rare* – throat pain, back tightness, head heaviness, moniliasis, throat tightness, leg rigidity, neck tightness, Mendelson's syndrome, heat stroke. *Cardiovascular System: Frequent* – hypertension, tachycardia, hypotension, bradycardia; *Infrequent* – palpitation, hemorrhage, myocardial infarction, prolonged QT interval, cardiac arrest, atrial fibrillation, heart failure, AV block, myocardial ischemia, phlebitis, deep vein thrombosis, angina pectoris, extrasystoles; *Rare* – vasovagal reaction, cardiomegaly, atrial flutter, thrombophlebitis. *Digestive System: Frequent – anorexia, nausea and vomiting; Infrequent* - increased appetite, gastroenteritis, dysphagia, flatulence, gastritis, tooth caries, gingivitis, hemorrhoids, gastroesophageal reflux, gastrointestinal hemorrhage, periodontal abscess, tongue edema, fecal incontinence, colitis, rectal hemorrhage, stomatitis, mouth ulcer, cholecystitis, fecal impaction, oral moniliasis, cholelithiasis, eructation, intestinal obstruction, peptic ulcer; *Rare* – esophagitis, gum hemorrhage, glossitis, hematemesis, melena, duodenal ulcer, cheilitis, hepatitis, hepatomegaly, pancreatitis, intestinal perforation. *Endocrine System: Infrequent* – hypothyroidism; *Rare* – goiter, hyperthyroidism. *Hemic/Lymphatic System: Frequent* – ecchymosis, anemia; *Infrequent* – hypochromic anemia, leukopenia, leukocytosis, lymphadenopathy, thrombocytopenia; *Rare* – eosinophilia, thrombocythemia, macrocytic anemia. *Metabolic and Nutritional Disorders: Frequent* – weight loss, creatine phosphokinase increased; *Infrequent* – dehydration, edema, hypercholesteremia, hyperglycemia, hypokalemia, diabetes mellitus, SGPT increased, hyperlipemia, hypoglycemia, thirst, BUN increased, hyponatremia, SGOT increased, alkaline phosphatase increased, iron deficiency anemia, creatinine increased, bilirubinemia, lactic dehydrogenase increased, obesity; *Rare* – hyperkalemia, gout, hypernatremia, cyanosis, hyperuricemia, hypoglycemic reaction. *Musculoskeletal System: Frequent* – muscle cramp, *Infrequent* – arthralgia, bone pain, myasthenia, arthritis, arthrosis, muscle *weakness, spasm, bursitis; Rare – rhabdomyolysis, tendonitis, tenosynovitis,* rheumatoid arthritis, myopathy. *Nervous System: Frequent* – depression, nervousness, increased salivation, hostility, suicidal thought, manic reaction, abnormal gait, confusion, cogwheel rigidity; *Infrequent* – dystonia, twitch, impaired concentration, paresthesia, vasodilation, hypesthesia, extremity tremor, impotence, bradykinesia, decreased libido, panic attack, apathy, dyskinesia, hypersomnia, vertigo, dysarthria, tardive dyskinesia, ataxia, impaired memory, stupor, increased libido, amnesia, cerebrovascular accident, hyperactivity, depersonalization, hypokinesia, restless leg, myoclonus, dysphoria, neuropathy, increased reflexes, slowed thinking, hyperkinesia, hyperesthesia, hypotonia, oculogyric crisis; *Rare – delirium, euphoria, buccoglossal syndrome, akinesia, blunt*ed affect, decreased consciousness, incoordination, cerebral ischemia, decreased reflexes, obsessive thought, intracranial hemorrhage. *Respiratory System: Frequent* – dyspnea, pneumonia; *Infrequent* – asthma, epistaxis, hiccup, laryngitis; *Rare* – hemoptysis, aspiration pneumonia, increased sputum, dry nasal passages, pulmonary edema, pulmonary embolism, hypoxia, respiratory failure, apnea. *Skin and Appendages: Frequent* – dry skin, pruritus, sweating, skin ulcer; *Infrequent* – acne, vesiculobullous rash, eczema, alopecia, psoriasis, seborrhea; *Rare* – maculopapular rash, exfoliative dermatitis, urticaria. *Special Senses: Frequent* – conjunctivitis, ear pain; *Infrequent* – dry eye, eye pain, tinnitus, otitis *media, cataract, altered taste, blepharitis; Rare – increased lacrimation, frequent* blinking, otitis externa, amblyopia, deafness, diplopia, eye hemorrhage, photophobia. *Urogenital System: Frequent* – urinary incontinence; *Infrequent* – cystitis, urinary frequency, leukorrhea, urinary retention, hematuria, dysuria, amenorrhea, abnormal ejaculation, vaginal hemorrhage, vaginal moniliasis, kidney failure, uterus hemorrhage, menorrhagia, albuminuria, kidney calculus, nocturia, polyuria, urinary urgency; *Rare* – breast pain, cervicitis, female lactation, anorgasmy, urinary burning, glycosuria, gynecomastia, urolithiasis, priapism.

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 ventila*tion, 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%.

DRUG ABUSE AND DEPENDENCE

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

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