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58 EDITION

2004

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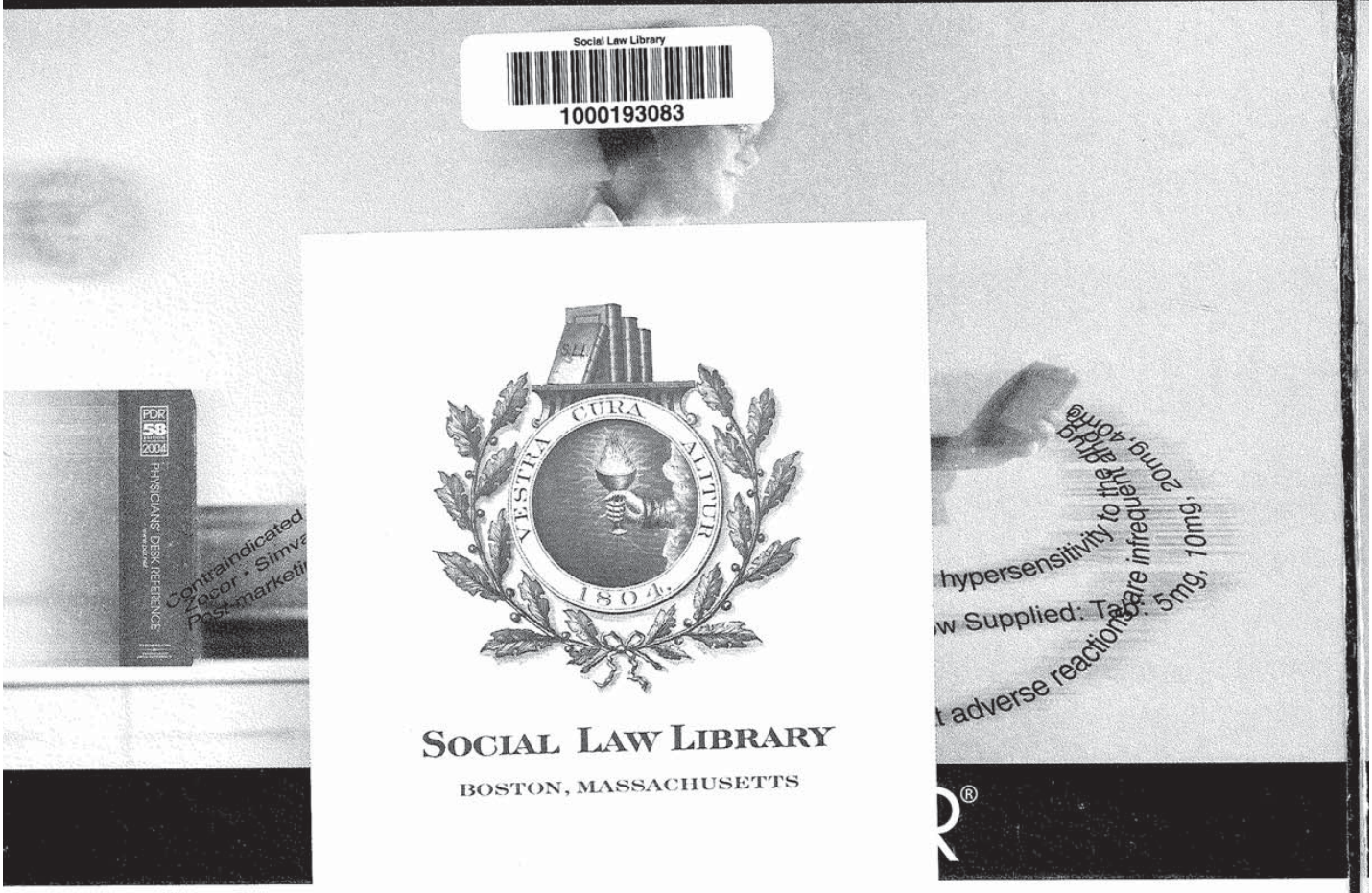

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PDR®
58
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2004

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FOREWORD TO THE FIFTY-EIGHTH EDITION

PDR enters its fifty-eighth year offering a wider array of pharmaceutical reference options than ever before. Long available unabridged—in print, on CD-ROM, and via the Internet—*PDR* now provides essential prescribing information in other forms as well.

About This Book

Physicians' Desk Reference is published by Thomson PDR in cooperation with participating manufacturers. The *PDR* contains Food and Drug Administration (FDA)-approved labeling for drugs as well as prescription information provided by manufacturers for grandfathered drugs and other drugs marketed without FDA approval under current FDA policies. Some dietary supplements and other products are also included.

Each full-length entry provides you with an exact copy of the product's FDA-approved or other manufacturer-supplied labeling. Under the Federal Food, Drug and Cosmetic (FD&C) Act, a drug approved for marketing may be labeled, promoted, and advertised by the manufacturer for only those uses for which the drug's safety and effectiveness have been established. The Code of Federal Regulations Title 21 Section 201.100(d)(1) pertaining to labeling for prescription products requires that for *PDR* content "indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant warnings, hazards, contraindications, side effects, and precautions" must be *"same in language and emphasis"* as the approved labeling for the products. The FDA regards the words *same in language and emphasis* as requiring VERBATIM use of the approved labeling providing such information. Furthermore, information that is emphasized in the approved labeling by the use of type set in a box, or in capitals, boldface, or italics, must be given the same emphasis in PDR.

The FDA has also recognized that the FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. The FDA also observes that accepted medical practice includes drug use that is not reflected in approved drug labeling. In the case of over-the-counter dietary supplements, it should be remembered that this information has not been evaluated by the Food and Drug Administration, and that such products are not intended to diagnose, treat, cure, or prevent any disease.

The function of the publisher is the compilation, organization, and distribution of this information. Each product description has been prepared by the manufacturer, and edited and approved by the manufacturer's medical department, medical director, and/or medical consultant. In organizing and presenting the material in *Physicians' Desk Reference*, the publisher does not warrant or guarantee any of the products described, or perform any independent analysis in connection with any of the product information contained herein. *Physicians' Desk Reference* does not assume, and expressly disclaims, any obligation to obtain and include any information other than that provided to it by the manufacturer. It should be understood that by making this material available, the publisher is not advocating the use of any product described herein, nor is the publisher responsible for misuse of a product due to typographical error. Additional information on any product may be obtained from the manufacturer.

Other Clinical Information Products from PDR

For complicated cases and special patient problems, there is no substitute for the in-depth data contained in *Physicians' Desk Reference*. But on other occasions, you may find that the **PDR® Monthly Prescribing Guide™** provides a handy alternative. With concise summaries of the FDA-approved and other manufacturer-supplied labeling found in *PDR*, this 350-page digest-sized reference presents certain key facts on more than 1,000 drugs, including the form, strength, and route; therapeutic class; approved indications; dosage; contraindications; warnings; precautions; pregnancy rating; drug interactions; and adverse reactions. Each entry alerts you to significant precautions you need to take, spells out the most common or dangerous adverse effects, summarizes the recommended adult and pediatric dosages, and supplies you with the *PDR* page number to turn to for further information. A full color insert of pill and product images allows you to correctly identify each product. Issued monthly, the guide is regularly updated, with detailed descriptions of the new drugs to receive FDA approval, as well as providing FDA-approved revisions to existing product information. In addition, you'll receive bulletins about major new developments on the pharmaceutical scene, an overview of important new agents nearing approval, a heads-up on the latest pharmaceutical issues to hit the consumer media, in-depth analysis of the common nutritional supplements that patients are taking, and a handy reminder of upcoming medical meetings. In fact, in one neat package you'll find the critical information you need to make a prescribing decision—with confidence that you're acting on the latest information available. To order your personal subscription to this important free monthly publication, simply call 1-800-232-7379.

If you prefer to carry drug information with you on a handheld device like a Palm® or Pocket PC, you will want to know about **mobilePDR®**. This easy-to-use software allows you to retrieve in an instant concise summaries of the FDA-approved and other manufacturer-supplied labeling for 1,500 of the most frequently prescribed drugs, lets you run automatic interaction checks on multidrug regimens, and even alerts you to significant changes in drug labeling, usually within 24 to 48 hours of announcements. You can look up drugs by brand or generic name,

by indication, and by therapeutic class. The drug interaction checker allows you to screen for interactions between as many as 32 drugs. The What's New feature provides daily alerts about drug recalls, labeling changes, new drug introductions, and so on. This portable electronic reference is updated daily with the latest available FDA-approved revisions to existing product information, plus the essential facts you need to make prescribing decisions for newly approved agents. Sync anytime, day or night, at your convenience, to be sure you have the most recent information available. Our auto-update feature updates the content and the software, so upgrades are easy to manage. *mobilePDR®* works with both the Palm and Windows CE operating systems, and it's free to U.S.-based MDs, DOs, NPs, and PAs in full-time patient practice and to medical students and residents. Check it out today at www.PDR.net.

For those who prefer to view drug information on the Internet, **PDR.net** is the best online source for comprehensive FDA-approved and other manufacturer-supplied labeling information, as found in *PDR*. Updated monthly, this incredible resource allows you to look up drugs by brand or generic name, by key word, or by indication, side effect, contraindication, or manufacturer. The drug interaction checker allows you to screen for interactions between as many as 20 different drugs. The site provides an index that can be searched to find comparable drugs. As a terrific extra benefit, images of all products are included for easy identification. Finally, as an added benefit, *PDR.net* hosts the download for *mobilePDR®*. At this one website, you get two great *PDR* products in one. In addition to all this, *PDR.net* provides links to such useful information as *Stedman's Medical Dictionary*, MEDLINE, online CME programs, clinical trials registries, evidence-based treatment decision tools, medical newsletters, Internet directories, online formularies, and the FDA's Medwatch. A wealth of information all in one place! Registration for *PDR.net* is free for U.S.-based MDs, DOs, NPs, and PAs in full-time patient practice as well as for medical students and residents. Visit www.PDR.net today to register.

For those times when all you need is quick confirmation of a particular dosage, you will want to have a copy of the **2004 PDR Pharmacopoeia™ Pocket Dosing Guide**. This handy little book can accompany you wherever you need to go, around the office or on hospital rounds. Only slightly larger than an index card and a half inch thick, it fits easily into any pocket, while providing you with FDA-approved dosing recommendations for more than 1,500 drugs. Unlike other condensed drug references, the information is drawn almost exclusively from the FDA-approved drug labeling published in *Physicians' Desk Reference*. And its tabular presentation makes lookups a breeze. The *2004 PDR Pharmacopoeia™ Pocket Dosing Guide* is a tool you really can't afford to be without.

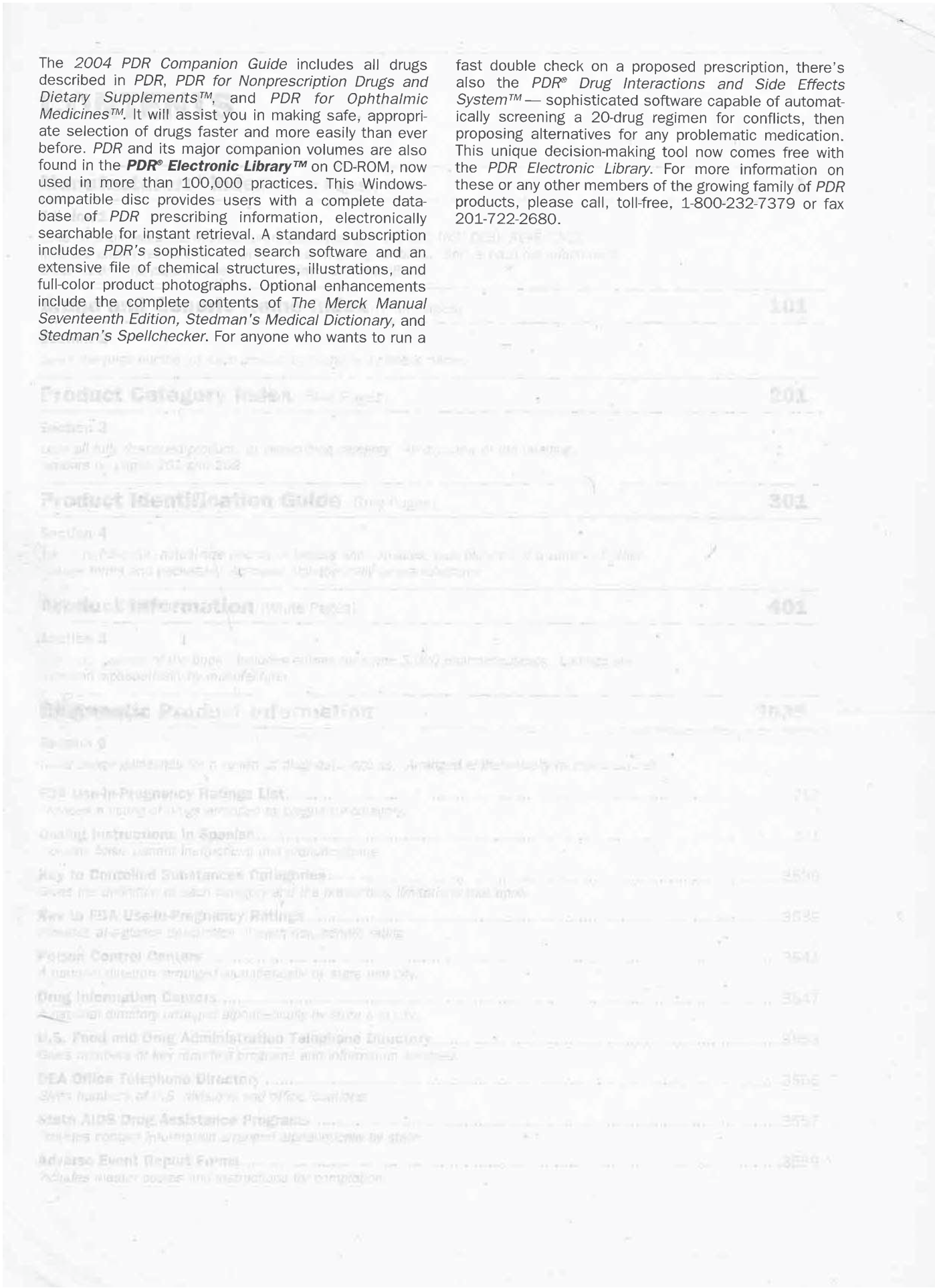
The use of over-the-counter nutritional supplements has skyrocketed, and *PDR* can help you to learn more about this unfamiliar—even exotic—set of agents. **PDR® for Nutritional Supplements™** offers the latest scientific consensus on hundreds of popular supplement products, including an array of amino acids, co-factors, fatty acids, probiotics, phytoestrogens, phytosterols, over-the-counter hormones, hormonal precursors, and much more. Focused on the scientific evidence for each supplement's claims, this unique reference offers you today's most detailed, informed, and objective overview of a burgeoning new area in the field of self-treatment. To protect your patients and ensure that they use only truly beneficial products, this book is a must.

For counseling patients who favor herbal remedies, another *PDR* reference may prove equally valuable. The very popular **PDR® for Herbal Medicines™** provides you with the latest science-based assessment of some 700 botanicals. Indexed by scientific, common, and brand names (as well as Western, Asian, and homeopathic indications), this volume also includes a Side Effects Index, a Drug/Herb Interactions Guide, an Herb Identification Guide with nearly 400 color photos, and a Safety Guide that lists herbs to be avoided during pregnancy and herbs to be used only under professional supervision. Although botanical products are not officially regulated or monitored in the United States, *PDR for Herbal Medicines* provides you with authoritative information—the findings of the German Medicines Agency's expert committee on herbal medicines, Commission E.

To maximize the value of *PDR* itself, you'll also need a copy of the 2004 edition of the **PDR Companion Guide™**, a 1,700-page reference that augments *PDR* with nine unique decision-making tools:

- *Interactions Index* identifies pharmaceuticals and foods capable of interacting with a chosen medication.
- *Food Interactions Cross-Reference* lists drugs that may interact with a given dietary item.
- *Side Effects Index* pinpoints pharmaceuticals associated with each of 3,600 distinct adverse reactions.
- *Indications Index* presents a broad range of therapeutic options for any given diagnosis.
- *Off-Label Treatment Guide* lists medications routinely used—but never officially approved—for treatment of nearly 1,000 specific disorders.
- *Contraindications Index* lists drugs to avoid in the presence of any given medical condition.
- *International Drug Name Index* names the U.S. equivalents of some 15,000 foreign medications.
- *Generic Availability Guide* shows which forms and strengths of a brand-name drug are also available generically.
- *Imprint Identification Guide* enables you to establish the nature of any unknown tablet or capsule by matching its imprint against an exhaustive catalog of identifying codes.

The *2004 PDR Companion Guide* includes all drugs described in *PDR*, *PDR for Nonprescription Drugs and Dietary Supplements™*, and *PDR for Ophthalmic Medicines™*. It will assist you in making safe, appropriate selection of drugs faster and more easily than ever before. *PDR* and its major companion volumes are also found in the ***PDR® Electronic Library™*** on CD-ROM, now used in more than 100,000 practices. This Windows-compatible disc provides users with a complete database of *PDR* prescribing information, electronically searchable for instant retrieval. A standard subscription includes *PDR's* sophisticated search software and an extensive file of chemical structures, illustrations, and full-color product photographs. Optional enhancements include the complete contents of *The Merck Manual Seventeenth Edition, Stedman's Medical Dictionary,* and *Stedman's Spellchecker*. For anyone who wants to run a fast double check on a proposed prescription, there's also the *PDR® Drug Interactions and Side Effects System™* — sophisticated software capable of automatically screening a 20-drug regimen for conflicts, then proposing alternatives for any problematic medication. This unique decision-making tool now comes free with the *PDR Electronic Library*. For more information on these or any other members of the growing family of *PDR* products, please call, toll-free, 1-800-232-7379 or fax 201-722-2680.



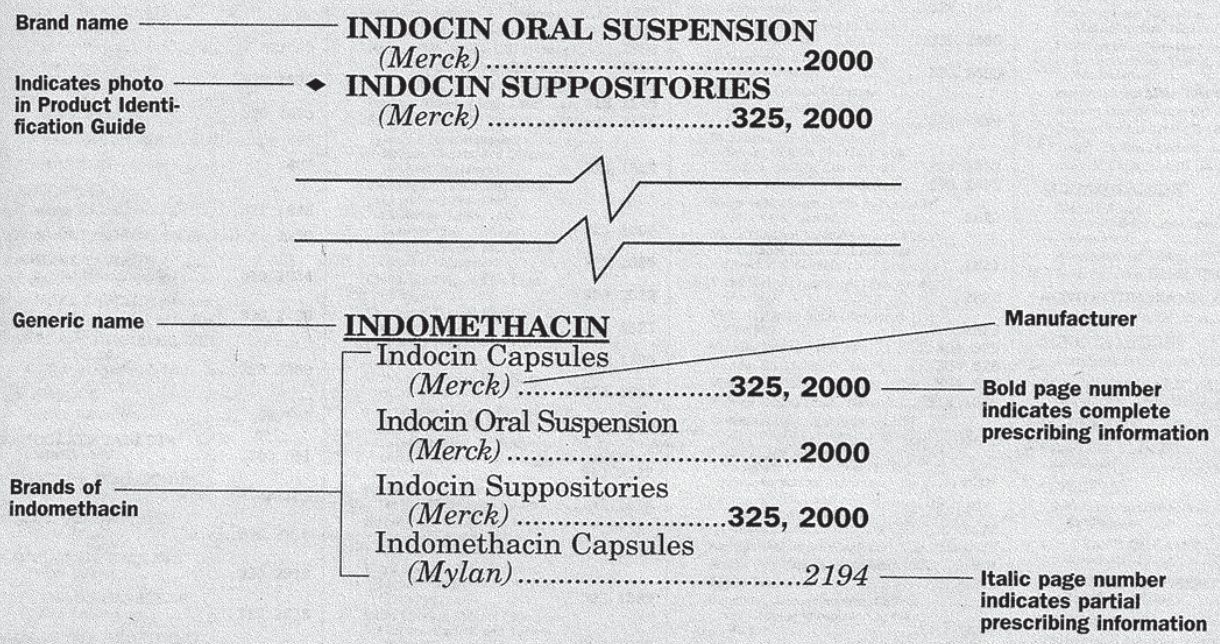
CONTENTS

HOW TO USE THE BRAND AND GENERIC NAME INDEX

This index lists every product alphabetically by both brand and generic name. Generic names are underlined; brand names are not.

Under each generic name, you will find a list of the brands that contain it. This enables you to find a particular product by either of its names. For example, "Indocin Oral Suspension" is listed once alphabetically and again under its generic name, indomethacin.

Each time a brand name appears, it is followed by the manufacturer's name and the page to consult for further information. Under a generic heading, all fully described brands are listed first, followed by those with only partial information. In each case, the brands are listed alphabetically.



BRAND AND GENERIC NAME INDEX

This index includes all entries in the Product Information and Diagnostic Product Information sections. Products are listed alphabetically by both brand and generic name. Generic names are underlined; brand names are not. Under each generic name, you will find a list of the brands that contain it. This enables you to find a product by either of its names. For example, the brand Ativan appears once in the A's, and again under its generic name, lorazepam.

Each time a brand name appears, it is followed by the manufacturer's name and the page number to consult for further information. If multiple page numbers appear, the first ones refer to photos of the product, the last one to its prescribing information. Under a generic heading, all fully described brands are listed first, followed by those with only partial information.

- **Bold page numbers** indicate full prescribing information.
- *Italic page numbers* signify partial information.
- The ◆ symbol marks drugs shown in the Product Identification Guide.
- The 📖 symbol means product information is located in *PDR For Nonprescription Drugs and Dietary Supplements*™.
- The ⊙ symbol means product information is located in *PDR For Ophthalmic Medicines*™.

B

GoLytely/NuLytely—Cont.

Each jug contains:
NuLYTELY: polyethylene glycol 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, potassium chloride 1.48 g. When made up to 4 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L.
Cherry NuLYTELY: polyethylene glycol 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, potassium chloride 1.48 g and flavoring ingredients 2.0 g. When made up to 4 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L.
Lemon-Lime NuLYTELY: polyethylene glycol 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, potassium chloride 1.48 g and flavoring ingredients 2.0 g. When made up to 4 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L.
Orange NuLYTELY: polyethylene glycol 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, potassium chloride 1.48 g and flavoring ingredients 2.0 g. When made up to 4 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/L.

STORAGE: Store in sealed container at 25°C. When reconstituted, keep solution refrigerated. Use within 48 hours. Discard unused portion.

GoLYTELY	NDC 52268-100-01
GoLYTELY 1 Gallon Packet	NDC 52268-700-01
Pineapple Flavor GoLYTELY	NDC 52268-101-01
NuLYTELY	NDC 52268-300-01
Cherry Flavor NuLYTELY	NDC 52268-301-01
Lemon-Lime Flavor NuLYTELY	NDC 52268-302-01
Orange Flavor NuLYTELY	NDC 52268-303-01

Rx only
Distributed by Braintree Laboratories, Inc., Braintree, MA 02185

Shown in Product Identification Guide, page 310

MIRALAX™ ℞

[mira 'lăx]
Polyethylene Glycol 3350, NF Powder for Solution
Full Prescribing Information

DESCRIPTION
A white powder for reconstitution. MiraLax (polyethylene glycol 3350, NF powder for solution) is a synthetic polyglycol having an average molecular weight of 3350. The actual molecular weight is not less than 90.0 percent and not greater than 110.0 percent of the nominal value. The chemical formula is $HO(C_2H_4O)_nH$ in which n represents the average number of oxyethylene groups. Below 55°C it is a free flowing white powder freely soluble in water. MiraLax is an osmotic agent for the treatment of constipation.

CLINICAL PHARMACOLOGY
Pharmacology: MiraLax is an osmotic agent which causes water to be retained with the stool. Essentially, complete recovery of MiraLax was shown in normal subjects without constipation. Attempts at recovery of MiraLax in constipated patients resulted in incomplete and highly variable recovery. In vitro study showed indirectly that MiraLax was not fermented into hydrogen or methane by the colonic microflora in human feces. MiraLax appears to have no effect on the active absorption or secretion of glucose or electrolytes. There is no evidence of tachyphylaxis.

CLINICAL TRIALS
In one study, patients with less than 3 bowel movements per week were randomized to MiraLax, 17 grams, or placebo for 14 days. An increase in bowel movement frequency was observed for both treatment groups during the first week of treatment. MiraLax was statistically superior to placebo during the second week of treatment.
In another study, patients with 3 bowel movements or less per week and/or less than 300 grams of stool per week were randomized to 2 dose levels of MiraLax or placebo for 10 days each. Success was defined by an increase in both bowel movement frequency and daily stool weight. For both parameters, superiority of the 17 gram dose of MiraLax over placebo was demonstrated.

INDICATIONS AND USAGE
For the treatment of occasional constipation. This product should be used for 2 weeks or less or as directed by a physician.

CONTRAINDICATIONS
MiraLax is contraindicated in patients with known or suspected bowel obstruction and patients known to be allergic to polyethylene glycol.

WARNINGS
Patients with symptoms suggestive of bowel obstruction (nausea, vomiting, abdominal pain or distention) should be evaluated to rule out this condition before initiating MiraLax therapy.

PRECAUTIONS
General: Patients presenting with complaints of constipation should have a thorough medical history and physical examination to detect associated metabolic, endocrine and neurogenic conditions, and medications. A diagnostic evaluation should include a structural examination of the colon. Patients should be educated about good defecatory and eating habits (such as high fiber diets) and lifestyle changes (adequate dietary fiber and fluid intake, regular exercise) which may produce more regular bowel habits.
MiraLax should be administered after being dissolved in approximately 8 ounces of water, juice, soda, coffee, or tea.
Information for Patients: MiraLax softens the stool and increases the frequency of bowel movements by retaining water in the stool. It should always be taken by mouth after being dissolved in 8 ounces of water, juice, soda, coffee, or tea. Should unusual cramps, bloating, or diarrhea occur, consult your physician.
Two to 4 days may be required to produce a bowel movement. This product should be used for 2 weeks or less or as directed by a physician. Prolonged, frequent or excessive use of MiraLax may result in electrolyte imbalance and dependence on laxatives.
Laboratory Tests: No clinically significant effects on laboratory tests have been demonstrated.
Drug Interactions: No specific drug interactions have been demonstrated.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term carcinogenicity studies, genetic toxicity studies and reproductive toxicity studies in animals have not been performed with MiraLax.
Pregnancy: Category C. Animal reproductive studies have not been performed with MiraLax. It is also not known whether MiraLax can cause fetal harm when administered to a pregnant woman, or can effect reproductive capacity. MiraLax should only be administered to a pregnant woman if clearly needed.
Pediatric Use: Safety and effectiveness in pediatric patients has not been established.
Geriatric Use: There is no evidence for special considerations when MiraLax is administered to elderly patients. In geriatric nursing home patients a higher incidence of diarrhea occurred at the recommended 17 gram dose. If diarrhea occurs MiraLax should be discontinued.

ADVERSE REACTIONS
Nausea, abdominal bloating, cramping and flatulence may occur. High doses may produce diarrhea and excessive stool frequency, particularly in elderly nursing home patients. Patients taking other medications containing polyethylene glycol have occasionally developed urticaria suggestive of an allergic reaction.

OVERDOSAGE
There have been no reports of accidental overdosage. In the event of overdosage diarrhea would be the expected major event. If an overdose of drug occurred without concomitant ingestion of fluid, dehydration due to diarrhea may result. Medication should be terminated and free water administered. The oral LD_{50} is >50 gm/Kg in mice, rats and rabbits.

DOSAGE AND ADMINISTRATION
The usual dose is 17 grams (about 1 heaping tablespoon) of powder per day (or as directed by physician) in 8 ounces of water, juice, soda, coffee, or tea. Each bottle of MiraLax is supplied with a measuring cap marked to contain 17 grams of laxative powder when filled to the indicated line.
Two to 4 days (48 to 96 hours) may be required to produce a bowel movement.

HOW SUPPLIED
In powdered form, for oral administration after dissolution in water, juice, soda, coffee, or tea. MiraLax is available in three package sizes; a 14 oz. container of 255 grams of laxative powder, a 26 oz. container of 527 grams of laxative powder, and a carton of 12 individual packets containing a single 17 g dose.
The cap on each bottle is marked with a measuring line and may be used to measure a single MiraLax dose of 17 grams (about 1 heaping tablespoon).
Each individual packet contains a single MiraLax dose of 17 grams (about 1 heaping tablespoon).
Rx only
STORAGE
Store at 25 degrees C (77 degrees F); excursions permitted to 15–30 degrees C (59–86 degrees F). See USP "Controlled Room Temperature."
Distributed by Braintree Laboratories, Inc., Braintree, MA 02185

D 6/01

Shown in Product Identification Guide, page 310

Check the **PINK** section
to find a particular **BRAND**
or generic.

Bristol-Myers Squibb Company
P.O. BOX 4500
PRINCETON, NJ 08543-4500

For Medical Information Contact:
Generally:
Bristol-Myers Squibb Drug Information Department
P.O. Box 4500
Princeton, NJ 08543-4500
(800) 321–1335

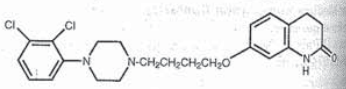
Adverse Drug Experiences
and Product Defects Reporting call
between 8:30 AM–4:30 PM EST:
(609) 818-3737

Sales and Ordering:
Orders may be placed by:
1. Calling your purchase orders toll-free between 8:30 AM–5:00 PM EST:
(800) 631-5244
2. Mailing your purchase orders to:
Bristol-Myers Squibb U.S. Pharmaceuticals
Attn: Customer Service
P.O. Box 5250
Princeton, NJ 08543-5250
3. Faxing your purchase orders to:
(800) 523-2965
4. Transmitting computer-to-computer on the NWDA and UCS formats through Ordernet Services use: DEA#PE0048579

ABILIFY™ ℞

[ă-bĭl-ĭfī]
(aripiprazole) Tablets
℞ only

DESCRIPTION
ABILIFY™ (aripiprazole) is a psychotropic drug that is available as tablets for oral administration. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The chemical structure is:



ABILIFY tablets are available in 5-mg, 10-mg, 15-mg, 20-mg, and 30-mg strengths. Inactive ingredients include lactose monohydrate, cornstarch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K_i=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50} >1000 nM). Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor.
The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole, e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha$_1$ receptors.
Pharmacokinetics
ABILIFY activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D_2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.
Absorption
Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. ABILIFY can be administered with or without food. Administration of a 15-mg ABILIFY tablet with a standard high-fat meal did not significantly affect the C_{max} or AUC of aripiprazole or its

active metabolite, dehydro-aripiprazole, but delayed T_{max} by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent D_2-receptor occupancy indicating brain penetration of aripiprazole in humans.

Metabolism and Elimination

Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Coadministration of ABILIFY (aripiprazole) with known inhibitors of CYP2D6, like quinidine in EMs, results in a 112% increase in aripiprazole plasma exposure, and dosing adjustment is needed (see **PRECAUTIONS: Drug-Drug Interactions**). The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs, respectively. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Following a single oral dose of [^{14}C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

Special Populations

In general, no dosage adjustment for ABILIFY is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function (see **DOSAGE AND ADMINISTRATION: Dosage in Special Populations**). The pharmacokinetics of aripiprazole in special populations are described below.

Hepatic Impairment

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

Renal Impairment

In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

Elderly

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients (see **PRECAUTIONS: Geriatric Use**).

Gender

C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

Smoking

Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

Drug-Drug Interactions

Potential for Other Drugs to Affect ABILIFY (aripiprazole)

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.

Potential for ABILIFY (aripiprazole) to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **PRECAUTIONS: Drug-Drug Interactions**).

Aripiprazole had no clinically important interactions with the following drugs:

Famotidine: Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40-mg single dose of the H_2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the C_{max} of aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

Valproate: When valproate (500–1500 mg/day) and aripiprazole (30 mg/day) were coadministered at steady state, the C_{max} and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

Lithium: A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200–1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C_{max} and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

Dextromethorphan: Aripiprazole at doses of 10 to 30 mg per day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway known to be dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methyoxymorphan, a pathway known to be dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole.

Warfarin: Aripiprazole 10 mg per day for 14 days had no effect on the pharmacokinetics of R- and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

Omeprazole: Aripiprazole 10 mg per day for 15 days had no effect on the pharmacokinetics of a single 20-mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with aripiprazole.

Clinical Studies

The efficacy of ABILIFY (aripiprazole) in the treatment of schizophrenia was evaluated in four short-term (4- and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Three of the four trials were able to distinguish aripiprazole from placebo, but one study, the smallest, did not. Three of these studies also included an active control group consisting of either risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for a comparison of ABILIFY and the active comparators.

In the three positive trials for ABILIFY, four primary measures were used for assessing psychiatric signs and symptoms. The Positive and Negative Syndrome Scale (PANSS) is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. The PANSS positive subscale is a subset of items in the PANSS that rates seven positive symptoms of schizophrenia (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility). The PANSS negative subscale is a subset of items in the PANSS that rates seven negative symptoms of schizophrenia (blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, stereotyped thinking). The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n=414) comparing two fixed doses of ABILIFY (15 or 30 mg/day) and haloperidol (10 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, and CGI-severity score. In addition, the 15-mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n=404) comparing two fixed doses of ABILIFY (20 or 30 mg/day) and risperidone (6 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of ABILIFY (10, 15, or 20 mg/day) to placebo, all three doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, and the PANSS negative subscale.

In a fourth study, a 4-week trial (n=103) comparing ABILIFY in a range of 5 to 30 mg/day or haloperidol 5 to 20 mg/day to placebo, haloperidol was superior to placebo, in the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis, and in a responder analysis based on the CGI-severity score, the primary outcomes for that trial. ABILIFY was only significantly different compared to placebo in a responder analysis based on the CGI-severity score.

Thus, the efficacy of 15-mg, 20-mg, and 30-mg daily doses was established in two studies for each dose, whereas the efficacy of the 10-mg dose was established in one study. There was no evidence in any study that the higher dose groups offered any advantage over the lowest dose group.

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

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 creatinine 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.

Continued on next page

Abilify—Cont.

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.

PRECAUTIONS

General

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY (aripiprazole) included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%); orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of 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 (aripiprazole) 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 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 discuss the following issues with patients for whom they prescribe ABILIFY (aripiprazole):

Interference with Cognitive and Motor Performance

Because aripiprazole may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely.

Pregnancy

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

Nursing

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

Concomitant Medication

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

Alcohol

Patients should be advised to avoid alcohol while taking ABILIFY.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Drug-Drug Interactions

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY (aripiprazole) 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 (aripiprazole).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2).

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

Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the *in vivo* micronucleus assay in mice, however, the response was shown to be due to a mechanism not considered relevant to humans.

Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

Pregnancy

Pregnancy Category C

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

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

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

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

Of the 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 (aripiprazole) in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 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 exposure. A total of 1887 aripiprazole-treated patients were treated for at least 180 days and 1251 aripiprazole-treated patients had at least 1 year of exposure.

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

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; ie, all reported events are included.

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

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

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

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

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

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

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks), 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.

Table 1: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials

Body System Adverse Event	Percentage of Patients Reporting Event[a] Aripiprazole (n=926)	 Placebo (n=413)
Body as a Whole		
Headache	32	25
Asthenia	7	5
Fever	2	1
Digestive System		
Nausea	14	10
Vomiting	12	7
Constipation	10	8
Nervous System		
Anxiety	25	24
Insomnia	24	19
Lightheadedness	11	7
Somnolence	11	8
Akathisia	10	7
Tremor	3	2
Respiratory System		
Rhinitis	4	3
Coughing	3	2
Skin and Appendages		
Rash	6	5
Special Senses		
Blurred vision	3	1

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

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

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials 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, 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 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.

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%)]. The following table 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 2: Weight Change Results Categorized by BMI at Baseline

	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 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.

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 5592 patients. All reported events are included except those already listed in Table 1, or other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of <0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

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

Body as a Whole: Frequent – flu syndrome, peripheral edema, chest pain, neck pain, neck rigidy; *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.

Continued on next page

Abilify—Cont.

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, blunted 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, pruritis, sweating, skin ulcer; *Infrequent* – acne, vesiculobullous rash, eczema, alopecia, psoriasis, seborrhea; *Rare* – maculopapular rash, exfoliative dermatitis, urticaria.
Special Senses: Frequent – conjunctivitus, 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.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILIFY (aripiprazole) is not a controlled substance.

Abuse and Dependence

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

OVERDOSAGE

Human Experience

In premarketing clinical studies, involving more than 5500 patients, accidental or intentional acute overdosage of aripiprazole was identified in seven patients. In the two patients taking the largest identified amount, 180 mg, the only symptoms reported were somnolence and vomiting in one of the two patients. In the patients who were evaluated in hospital settings, including the two patients taking 180 mg, there were no observations indicating an adverse change in vital signs, laboratory assessments, or ECG. An uneventful, accidental overdose (15 mg) occurred in a non-patient, an 18-month-old child, with concomitant ingestion of ATIVAN® (2 mg).

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 (aripiprazole), 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.

DOSAGE AND ADMINISTRATION

Usual Dose

The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day; however, doses higher than 10 or 15 mg/day, the lowest doses in these trials, were not more effective than 10 or 15 mg/day. Dosage increases should not be made before 2 weeks, the time needed to achieve steady state.

Dosage in Special Populations

Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status (see **CLINICAL PHARMACOLOGY: Special Populations**).
Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP3A4 inhibitors: When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.
Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP2D6 inhibitors: When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

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Dosage adjustment for patients taking potential CYP3A4 inducers: When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be doubled (to 20 to 30 mg). Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 to 15 mg.

Maintenance Therapy

There is no body of evidence available from controlled trials to answer the question of how long a patient treated with aripiprazole should remain on it. It is generally agreed, however, that pharmacological treatment for episodes of acute schizophrenia should continue for up to 6 months or longer. Patients should be periodically reassessed to determine the need for maintenance treatment.

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

ANIMAL TOXICOLOGY

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40- and 60-mg/kg doses represent 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m^2 and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

HOW SUPPLIED

ABILIFY™ (aripiprazole) Tablets are available in the following strengths and packages.

The 5-mg ABILIFY tablets are blue, modified rectangular tablets, debossed on one side with "A-007" and "5".

Bottles of 30	NDC 59148-007-13
Blister of 100	NDC 59148-007-35

The 10-mg ABILIFY tablets are pink, modified rectangular tablets, debossed on one side with "A-008" and "10".

Bottles of 30	NDC 59148-008-13
Blister of 100	NDC 59148-008-35

The 15-mg ABILIFY tablets are yellow, round tablets, debossed on one side with "A-009" and "15".

Bottles of 30	NDC 59148-009-13
Blister of 100	NDC 59148-009-35

The 20-mg ABILIFY tablets are white, round tablets, debossed on one side with "A-010" and "20".

Bottles of 30	NDC 59148-010-13
Blister of 100	NDC 59148-010-35

The 30-mg ABILIFY tablets are pink, round tablets, debossed on one side with "A-011" and "30".

Bottles of 30	NDC 59148-011-13
Blister of 100	NDC 59148-011-35

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 Co, Princeton, NJ 08543 USA
Manufactured by Otsuka Pharmaceutical Co, Ltd, Tokyo, 101-8535 Japan
Distributed by Bristol-Myers Squibb Co, Princeton, NJ 08543 USA
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Bristol-Myers Squibb Company
Princeton, NJ 08543 U.S.A.
Otsuka America
Pharmaceutical, Inc.
D6-B0001-06-03 Revised: May 2003
1156731A4 A4114/10-02

Shown in Product Identification Guide, page 310

AVALIDE®

℞

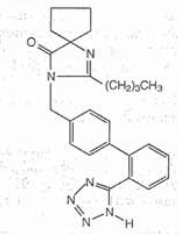
[avă-līde]
(irbesartan-hydrochlorothiazide)
Tablets
Rx only

USE IN PREGNANCY

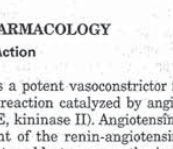
When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, AVALIDE should be discontinued as soon as possible. (See **WARNINGS: Fetal/Neonatal Morbidity and Mortality**.)

DESCRIPTION

AVALIDE®* (irbesartan-hydrochlorothiazide) Tablets is a combination of an angiotensin II receptor antagonist (AT_1 subtype), irbesartan, and a thiazide diuretic, hydrochlorothiazide (HCTZ).
Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-[[2′-(1*H*-tetrazol-5-yl) [1, 1′-biphenyl]-4-yl] methyl]-1,3-diazaspiro [4,4] non-1-en-4-one. Its empirical formula is $C_{25}H_{28}N_6O$, and its structural formula is:



Irbesartan is a white to off-white crystalline powder with a molecular weight of 428.5. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH of 7.4. Irbesartan is slightly soluble in alcohol and methylene chloride and practically insoluble in water.
Hydrochlorothiazide is 6-chloro-3,4-dihydro- 2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is:



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 297.7. Hydrochlorothiazide is slightly soluble in water and freely soluble in sodium hydroxide solution.
AVALIDE is available for oral administration in tablets containing 150 mg or 300 mg of irbesartan combined with 12.5 mg of hydrochlorothiazide. Inactive ingredients include: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, ferric oxide red, ferric oxide yellow, silicon dioxide, and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism Of Action

Irbesartan
Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal resorption of

ReoPro—Cont.

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Leiden, The Netherlands
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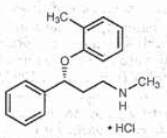
Eli Lilly and Company
Indianapolis, IN 46285
Revision Date: May 14, 2001
Shown in Product Identification Guide, page 322

STRATTERA™ ℞

[strä-tĕr-ă]
(atomoxetine HCl)

DESCRIPTION

STRATTERA™ (atomoxetine HCl) is a selective norepinephrine reuptake inhibitor. Atomoxetine HCl is the *R*(-) isomer as determined by x-ray diffraction. The chemical designation is (-)-*N*-methyl-3-phenyl-3-(*o*-tolyloxy)-propylamine hydrochloride. The molecular formula is $C_{17}H_{21}NO \bullet HCl$, which corresponds to a molecular weight of 291.82. The chemical structure is:



Atomoxetine HCl is a white to practically white solid, which has a solubility of 27.8 mg/mL in water.

STRATTERA capsules are intended for oral administration only.

Each capsule contains atomoxetine HCl equivalent to 10, 18, 25, 40, or 60 mg of atomoxetine. The capsules also contain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and other inactive ingredients. The capsule shells also contain one or more of the following: FD&C Blue No. 2, synthetic yellow iron oxide, titanium dioxide. The capsules are imprinted with edible black ink.

CLINICAL PHARMACOLOGY

Pharmacodynamics and Mechanism of Action

The precise mechanism by which atomoxetine produces its therapeutic effects in Attention-Deficit/Hyperactivity Disorder (ADHD) is unknown, but is thought to be related to selective inhibition of the pre-synaptic norepinephrine transporter, as determined in ex vivo uptake and neurotransmitter depletion studies.

Human Pharmacokinetics

Atomoxetine is well-absorbed after oral administration and is minimally affected by food. It is eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway and subsequent glucuronidation. Atomoxetine has a half-life of about 5 hours. A fraction of the population (about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity in this pathway resulting in 10-fold higher AUCs, 5-fold higher peak plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people with normal activity [extensive metabolizers (EMs)]. Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, and quinidine, cause similar increases in exposure.

The pharmacokinetics of atomoxetine have been evaluated in more than 400 children and adolescents in selected clinical trials, primarily using population pharmacokinetic studies. Single-dose and steady-state individual pharmacokinetic data were also obtained in children, adolescents, and adults. When doses were normalized to a mg/kg basis, similar half-life, C_{max}, and AUC values were observed in children, adolescents, and adults. Clearance and volume of distribution after adjustment for body weight were also similar.

Absorption and Distribution—Atomoxetine is rapidly absorbed after oral administration, with absolute bioavailability of about 63% in EMs and 94% in PMs. Maximal plasma concentrations (C_{max}) are reached approximately 1 to 2 hours after dosing.

STRATTERA can be administered with or without food. Administration of STRATTERA with a standard high-fat meal in adults did not affect the extent of oral absorption of atomoxetine (AUC), but did decrease the rate of absorption, resulting in a 37% lower C_{max}, and delayed T_{max} by 3 hours. In clinical trials with children and adolescents, administration of STRATTERA with food resulted in a 9% lower C_{max}.

The steady-state volume of distribution after intravenous administration is 0.85 L/kg indicating that atomoxetine distributes primarily into total body water. Volume of distribution is similar across the patient weight range after normalizing for body weight.

At therapeutic concentrations, 98% of atomoxetine in plasma is bound to protein, primarily albumin.

Metabolism and Elimination—Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Coadministration of STRATTERA with potent inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary (*see* Drug-Drug Interactions). Atomoxetine did not inhibit or induce the CYP2D6 pathway.

The major oxidative metabolite formed, regardless of CYP2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs).

Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 21.6 hours. For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of N-desmethylatomoxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34 to 40 hours).

Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-*O*-glucuronide, mainly in the urine (greater than 80% of the dose) and to a lesser extent in the feces (less than 17% of the dose). Only a small fraction of the STRATTERA dose is excreted as unchanged atomoxetine (less than 3% of the dose), indicating extensive biotransformation.

Special Populations

Hepatic insufficiency—Atomoxetine exposure (AUC) is increased, compared with normal subjects, in EM subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) hepatic insufficiency. Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency (*see* DOSAGE AND ADMINISTRATION).

Renal insufficiency—EM subjects with end stage renal disease had higher systemic exposure to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when exposure was corrected for mg/kg dose. STRATTERA can therefore be administered to ADHD patients with end stage renal disease or lesser degrees of renal insufficiency using the normal dosing regimen.

Geriatric—The pharmacokinetics of atomoxetine have not been evaluated in the geriatric population.

Pediatric—The pharmacokinetics of atomoxetine in children and adolescents are similar to those in adults. The pharmacokinetics of atomoxetine have not been evaluated in children under 6 years of age.

Gender—Gender did not influence atomoxetine disposition.

Ethnic origin—Ethnic origin did not influence atomoxetine disposition (except that PMs are more common in Caucasians).

Drug-Drug Interactions

CYP2D6 activity and atomoxetine plasma concentration—Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In EMs, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage adjustment of STRATTERA in EMs may be necessary when coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine (*see* Drug Interactions *under* PRECAUTIONS). In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

Effect of atomoxetine on P450 enzymes—Atomoxetine did not cause clinically important inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9.

Albuterol—Albuterol (600 mcg iv over 2 hours) induced increases in heart rate and blood pressure. These effects were potentiated by atomoxetine (60 mg BID for 5 days) and were most marked after the initial coadministration of albuterol and atomoxetine (*see* Drug-Drug Interactions *under* PRECAUTIONS).

Alcohol—Consumption of ethanol with STRATTERA did not change the intoxicating effects of ethanol.

Desipramine—Coadministration of STRATTERA (40 or 60 mg BID for 13 days) with desipramine, a model compound for CYP2D6 metabolized drugs (single dose of 50 mg), did not alter the pharmacokinetics of desipramine. No dose adjustment is recommended for drugs metabolized by CYP2D6.

Methylphenidate—Coadministration of methylphenidate with STRATTERA did not increase cardiovascular effects beyond those seen with methylphenidate alone.

Midazolam—Coadministration of STRATTERA (60 mg BID for 12 days) with midazolam, a model compound for CYP3A4 metabolized drugs, (single dose of 5 mg), resulted in 15% increase in AUC of midazolam. No dose adjustment is recommended for drugs metabolized by CYP3A.

Drugs highly bound to plasma protein—In vitro drug-displacement studies were conducted with atomoxetine and other highly-bound drugs at therapeutic concentrations. Atomoxetine did not affect the binding of warfarin, acetylsalicylic acid, phenytoin, or diazepam to human albumin. Similarly, these compounds did not affect the binding of atomoxetine to human albumin.

Drugs that affect gastric pH—Drugs that elevate gastric pH (magnesium hydroxide/aluminum hydroxide, omeprazole) had no effect on STRATTERA bioavailability.

CLINICAL STUDIES

The effectiveness of STRATTERA in the treatment of ADHD was established in 6 randomized, double-blind, placebo-controlled studies in children, adolescents, and adults who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD (*see* INDICATIONS AND USAGE).

Children and Adolescents

The effectiveness of STRATTERA in the treatment of ADHD was established in 4 randomized, double-blind, placebo-controlled studies of pediatric patients (ages 6 to 18). Approximately one-third of the patients met DSM-IV criteria for inattentive subtype and two-thirds met criteria for both inattentive and hyperactive/impulsive subtypes (*see* INDICATIONS AND USAGE).

Signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline to endpoint for STRATTERA- and placebo-treated patients using an intent-to-treat analysis of the primary outcome measure, the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS) total score including hyperactive/impulsive and inattentive subscales. Each item on the ADHDRS maps directly to one symptom criterion for ADHD in the DSM-IV.

In Study 1, an 8-week randomized, double-blind, placebo-controlled, dose-response, acute treatment study of children and adolescents aged 8 to 18 (N=297), patients received either a fixed dose of STRATTERA (0.5, 1.2, or 1.8 mg/kg/day) or placebo. STRATTERA was administered as a divided dose in the early morning and late afternoon/early evening. At the 2 higher doses, improvements in ADHD symptoms were statistically significantly superior in STRATTERA-treated patients compared with placebo-treated patients as measured on the ADHDRS scale. The 1.8-mg/kg/day STRATTERA dose did not provide any additional benefit over that observed with the 1.2-mg/kg/day dose. The 0.5-mg/kg/day STRATTERA dose was not superior to placebo.

In Study 2, a 6-week randomized, double-blind, placebo-controlled, acute treatment study of children and adolescents aged 6 to 16 (N=171), patients received either STRATTERA or placebo. STRATTERA was administered as

a single dose in the early morning and titrated on a weight-adjusted basis according to clinical response, up to a maximum dose of 1.5 mg/kg/day. The mean final dose of STRATTERA was approximately 1.3 mg/kg/day. ADHD symptoms were statistically significantly improved on STRATTERA compared with placebo, as measured on the ADHDRS scale. This study shows that STRATTERA is effective when administered once daily in the morning.

In 2 identical, 9-week, acute, randomized, double-blind, placebo-controlled studies of children aged 7 to 13 (Study 3, N=147; Study 4, N=144), STRATTERA and methylphenidate were compared with placebo. STRATTERA was administered as a divided dose in the early morning and late afternoon (after school) and titrated on a weight-adjusted basis according to clinical response. The maximum recommended STRATTERA dose was 2.0 mg/kg/day. The mean final dose of STRATTERA for both studies was approximately 1.6 mg/kg/day. In both studies, ADHD symptoms statistically significantly improved more on STRATTERA than on placebo, as measured on the ADHDRS scale.

Examination of population subsets based on gender and age (<12 and 12 to 17) did not reveal any differential responsiveness on the basis of these subgroupings. There was not sufficient exposure of ethnic groups other than Caucasian to allow exploration of differences in these subgroups.

Adults

The effectiveness of STRATTERA in the treatment of ADHD was established in 2 randomized, double-blind, placebo-controlled clinical studies of adult patients, age 18 and older, who met DSM-IV criteria for ADHD.

Signs and symptoms of ADHD were evaluated using the investigator-administered Conners Adult ADHD Rating Scale Screening Version (CAARS), a 30-item scale. The primary effectiveness measure was the 18-item Total ADHD Symptom score (the sum of the inattentive and hyperactivity/impulsivity subscales from the CAARS) evaluated by a comparison of mean change from baseline to endpoint using an intent-to-treat analysis.

In 2 identical, 10-week, randomized, double-blind, placebo-controlled acute treatment studies (Study 5, N=280; Study 6, N=256), patients received either STRATTERA or placebo. STRATTERA was administered as a divided dose in the early morning and late afternoon/early evening and titrated according to clinical response in a range of 60 to 120 mg/day. The mean final dose of STRATTERA for both studies was approximately 95 mg/day. In both studies, ADHD symptoms were statistically significantly improved on STRATTERA, as measured on the ADHD Symptom score from the CAARS scale.

Examination of population subsets based on gender and age (<42 and ≥42) did not reveal any differential responsiveness on the basis of these subgroupings. There was not sufficient exposure of ethnic groups other than Caucasian to allow exploration of differences in these subgroups.

INDICATIONS AND USAGE

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

The effectiveness of STRATTERA in the treatment of ADHD was established in 2 placebo-controlled trials in children, 2 placebo-controlled trials in children and adolescents, and 2 placebo-controlled trials in adults who met DSM-IV criteria for ADHD (*see* CLINICAL STUDIES).

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause impairment and that were present before age 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and must be present in 2 or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses things, easily distracted, forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming, leaving seat, inappropriate running/climbing, difficulty with quiet activities, "on the go," excessive talking, blurting answers, can't wait turn, intrusive. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

Special Diagnostic Considerations

The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but also of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

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

Long-term Use

The effectiveness of STRATTERA for long-term use, ie, for more than 9 weeks in child and adolescent patients and 10 weeks in adult patients, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use STRATTERA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Hypersensitivity

STRATTERA is contraindicated in patients known to be hypersensitive to atomoxetine or other constituents of the product (*see* WARNINGS).

Monoamine Oxidase Inhibitors (MAOI)

STRATTERA should not be taken with an MAOI, or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing STRATTERA. With other drugs that affect brain monoamine concentrations, there have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when taken in combination with an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Such reactions may occur when these drugs are given concurrently or in close proximity.

Narrow Angle Glaucoma

In clinical trials, STRATTERA use was associated with an increased risk of mydriasis and therefore its use is not recommended in patients with narrow angle glaucoma.

WARNINGS

Allergic Events

Although uncommon, allergic reactions, including angioneurotic edema, urticaria, and rash, have been reported in patients taking STRATTERA.

Growth

Growth should be monitored during treatment with STRATTERA. During acute treatment studies (up to 9 weeks), STRATTERA-treated patients lost an average of 0.4 kg, while placebo patients gained an average of 1.5 kg. In a controlled trial that randomized patients to placebo or 1 of 3 atomoxetine doses, 1.3%, 7.1%, 19.3%, and 29.1% of patients lost at least 3.5% of their body weight in the placebo, 0.5, 1.2, and 1.8 mg/kg/day STRATTERA dose groups, respectively. During acute treatment studies, STRATTERA-treated patients grew an average of 0.9 cm, while placebo-treated patients grew an average of 1.1 cm. There are no long-term, placebo-controlled data to evaluate the effect of STRATTERA on growth. Weight and height were assessed during open-label studies of 12 and 18 months, and mean rates of growth were compared to normal growth curves. Patients treated with STRATTERA for at least 18 months gained an average of 6.5 kg while mean weight percentile decreased slightly from 68 to 60. For this same group of patients, the average gain in height was 9.3 cm with a slight decrease in mean height percentile from 54 to 50. Among patients treated for at least 6 months, mean weight gain was lower for poor metabolizer (PM) patients compared with extensive metabolizer (EM) patients (+0.7 kg compared with +3.0 kg), while mean growth for PM patients was 4.3 cm and mean growth for EM patients was 4.4 cm. Whether final adult height or weight is affected by treatment with STRATTERA is unknown. Patients requiring long-term therapy should be monitored, and consideration should be given to interrupting therapy in patients who are not growing or gaining weight satisfactorily.

PRECAUTIONS

General

Effects on blood pressure and heart rate—STRATTERA should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease because it can increase blood pressure and heart rate. Pulse and blood pressure should be measured at baseline, following STRATTERA dose increases, and periodically while on therapy.

In pediatric placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase in heart rate of about 6 beats/minute compared with placebo subjects. At the final study visit before drug discontinuation, 3.6% (12/335) of STRATTERA-treated subjects had heart rate increases of at least 25 beats/minute and a heart rate of at least 110 beats/minute, compared with 0.5% (1/204) of placebo subjects. No pediatric subject had a heart rate increase of at least 25 beats/minute and a heart rate of at least 110 beats/minute on more than one occasion. Tachycardia was identified as an adverse event for 1.5% (5/340) of these pediatric subjects compared with 0.5% (1/207) of placebo subjects. The mean heart rate increase in extensive metabolizer (EM) patients was 6.7 beats/minute, and in poor metabolizer (PM) patients 10.4 beats/minute.

STRATTERA-treated pediatric subjects experienced mean increases of about 1.5 mm Hg in systolic and diastolic blood pressures compared with placebo. At the final study visit before drug discontinuation, 6.8% (22/324) of STRATTERA-treated pediatric subjects had high systolic blood pressure measurements compared with 3.0% (6/197) of placebo subjects. High systolic blood pressures were measured on 2 or more occasions in 8.6% (28/324) of STRATTERA-treated subjects and 3.6% (7/197) of placebo subjects. At the final study visit before drug discontinuation, 2.8% (9/326) of STRATTERA-treated pediatric subjects had high diastolic blood pressure measurements compared with 0.5% (1/200) of placebo subjects. High diastolic blood pressures were measured on 2 or more occasions in 5.2% (17/326) of STRATTERA-treated subjects and 1.5% (3/200) placebo subjects. (High systolic and diastolic blood pressure measurements were defined as those exceeding the 95th percentile, stratified by age, gender, and height percentile - National High Blood Pressure Education Working Group on Hypertension Control in Children and Adolescents.)

In adult placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase in heart rate of 5 beats/minute compared with placebo subjects. Tachycardia was identified as an adverse event for 3% (8/269) of these adult atomoxetine subjects compared with 0.8% (2/263) of placebo subjects.

STRATTERA-treated adult subjects experienced mean increases in systolic (about 3 mm Hg) and diastolic (about 1 mm Hg) blood pressures compared with placebo. At the final study visit before drug discontinuation, 1.9% (5/258) of STRATTERA-treated adult subjects had systolic blood pressure measurements ≥150 mm Hg compared with 1.2% (3/256) of placebo subjects. At the final study visit before drug discontinuation, 0.8% (2/257) of STRATTERA-treated adult subjects had diastolic blood pressure measurements ≥100 mm Hg compared with 0.4% (1/257) of placebo subjects. No adult subject had a high systolic or diastolic blood pressure detected on more than one occasion.

Orthostatic hypotension has been reported in subjects taking STRATTERA. In short-term child- and adolescent-controlled trials, 1.8% (6/340) of STRATTERA-treated subjects experienced symptoms of postural hypotension compared with 0.5% (1/207) of placebo-treated subjects. STRATTERA should be used with caution in any condition that may predispose patients to hypotension.

Effects on urine outflow from the bladder—In adult ADHD controlled trials, the rates of urinary retention (3%, 7/269) and urinary hesitation (3%, 7/269) were increased among atomoxetine subjects compared with placebo subjects (0%, 0/263). Two adult atomoxetine subjects and no placebo subjects discontinued from controlled clinical trials because of urinary retention. A complaint of urinary retention or urinary hesitancy should be considered potentially related to atomoxetine.

Information for Patients

Patients should read *Information for Patients* before starting therapy with STRATTERA and when the prescription is renewed.

Patients should consult a physician if they are taking or plan to take any prescription or over-the-counter medicines, dietary supplements, or herbal remedies.

Patients should consult a physician if they are nursing, pregnant, or thinking of becoming pregnant while taking STRATTERA.

Patients may take STRATTERA with or without food.

If patients miss a dose, they should take it as soon as possible, but should not take more than the prescribed total daily amount of STRATTERA in any 24-hour period.

Patients should use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by atomoxetine.

Laboratory Tests

Routine laboratory tests are not required.

CYP2D6 metabolism—Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA (*see* ADVERSE REACTIONS).

Drug-Drug Interactions:

Albuterol—STRATTERA should be administered with caution to patients being treated with systemically-administered (oral or intravenous) albuterol (or other $beta_2$ agonists) because the action of albuterol on the cardiovascular system can be potentiated.

CYP2D6 inhibitors—Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In EMs, selective inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage adjustment of STRATTERA may be necessary when coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine (*see* DOSAGE AND ADMINISTRATION). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and $C_{ss,max}$ is about 3- to 4-fold greater than atomoxetine alone.

In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

Continued on next page

* **Identi-Code® symbol. This product information was prepared in June 2002. Current information on these and other products of Eli Lilly and Company may be obtained by direct inquiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.**

Strattera—Cont.

Monoamine oxidase inhibitors— See CONTRAINDICATIONS.

Pressor agents—Because of possible effects on blood pressure, STRATTERA should be used cautiously with pressor agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis—Atomoxetine HCl was not carcinogenic in rats and mice when given in the diet for 2 years at time-weighted average doses up to 47 and 458 mg/kg/day, respectively. The highest dose used in rats is approximately 8 and 5 times the maximum human dose in children and adults, respectively, on a mg/m^2 basis. Plasma levels (AUC) of atomoxetine at this dose in rats are estimated to be 1.8 times (extensive metabolizers) or 0.2 times (poor metabolizers) those in humans receiving the maximum human dose. The highest dose used in mice is approximately 39 and 26 times the maximum human dose in children and adults, respectively, on a mg/m^2 basis.

Mutagenesis—Atomoxetine HCl was negative in a battery of genotoxicity studies that included a reverse point mutation assay (Ames Test), an in vitro mouse lymphoma assay, a chromosomal aberration test in Chinese hamster ovary cells, an unscheduled DNA synthesis test in rat hepatocytes, and an in vivo micronucleus test in mice. However, there was a slight increase in the percentage of Chinese hamster ovary cells with diplochromosomes, suggesting endoreduplication (numerical aberration).

The metabolite N-desmethylatomoxetine HCl was negative in the Ames Test, mouse lymphoma assay, and unscheduled DNA synthesis test.

Impairment of fertility—Atomoxetine HCl did not impair fertility in rats when given in the diet at doses of up to 57 mg/kg/day, which is approximately 6 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C—Pregnant rabbits were treated with up to 100 mg/kg/day of atomoxetine by gavage throughout the period of organogenesis. At this dose, in 1 of 3 studies, a decrease in live fetuses and an increase in early resorptions was observed. Slight increases in the incidences of atypical origin of carotid artery and absent subclavian artery were observed. These findings were observed at doses that caused slight maternal toxicity. The no-effect dose for these findings was 30 mg/kg/day. The 100-mg/kg dose is approximately 23 times the maximum human dose on a mg/m^2 basis; plasma levels (AUC) of atomoxetine at this dose in rabbits are estimated to be 3.3 times (extensive metabolizers) or 0.4 times (poor metabolizers) those in humans receiving the maximum human dose.

Rats were treated with up to approximately 50 mg/kg/day of atomoxetine (approximately 6 times the maximum human dose on a mg/m^2 basis) in the diet from 2 weeks (females) or 10 weeks (males) prior to mating through the periods of organogenesis and lactation. In 1 of 2 studies, decreases in pup weight and pup survival were observed. The decreased pup survival was also seen at 25 mg/kg (but not at 13 mg/kg). In a study in which rats were treated with atomoxetine in the diet from 2 weeks (females) or 10 weeks (males) prior to mating throughout the period of organogenesis, a decrease in fetal weight (female only) and an increase in the incidence of incomplete ossification of the vertebral arch in fetuses were observed at 40 mg/kg/day (approximately 5 times the maximum human dose on a mg/m^2 basis) but not at 20 mg/kg/day.

No adverse fetal effects were seen when pregnant rats were treated with up to 150 mg/kg/day (approximately 17 times the maximum human dose on a mg/m^2 basis) by gavage throughout the period of organogenesis.

No adequate and well-controlled studies have been conducted in pregnant women. STRATTERA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Parturition in rats was not affected by atomoxetine. The effect of STRATTERA on labor and delivery in humans is unknown.

Nursing Mothers

Atomoxetine and/or its metabolites were excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Caution should be exercised if STRATTERA is administered to a nursing woman.

Pediatric Use

The safety and efficacy of STRATTERA in pediatric patients less than 6 years of age have not been established. The efficacy of STRATTERA beyond 9 weeks and safety of STRATTERA beyond 1 year of treatment have not been systematically evaluated.

A study was conducted in young rats to evaluate the effects of atomoxetine on growth and neurobehavioral and sexual development. Rats were treated with 1, 10, or 50 mg/kg/day (approximately 0.2, 2, an 8 times, respectively, the maximum human dose on a mg/m^2 basis) of atomoxetine given by gavage from the early postnatal period (Day 10 of age) through adulthood. Slight delays in onset of vaginal patency (all doses) and preputial separation (10 and 50 mg/kg), slight decreases in epididymal weight and sperm number (10 and 50 mg/kg), and a slight decrease in corpora lutea (50 mg/kg) were seen, but there were no effects on fertility or reproductive performance. A slight delay in onset of incisor eruption was seen at 50 mg/kg. A slight increase in motor activity was seen on Day 15 (males at 10 and 50 mg/kg and females at 50 mg/kg) and on Day 30 (females at 50 mg/kg) but not on Day 60 of age. There were no effects on learning and memory tests. The significance of these findings to humans is unknown.

Geriatric Use

The safety and efficacy of STRATTERA in geriatric patients have not been established.

ADVERSE REACTIONS

STRATTERA was administered to 2067 children or adolescent patients with ADHD and 270 adults with ADHD in clinical studies. During the ADHD clinical trials, 169 patients were treated for longer than 1 year and 526 patients were treated for over 6 months.

The data in the following tables and text 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 data obtained from other clinical investigations involving different treatments, uses, or investigators. The cited data provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence in the population studied.

Child and Adolescent Clinical Trials

Reasons for discontinuation of treatment due to adverse events in child and adolescent clinical trials—In acute child and adolescent placebo-controlled trials, 3.5% (15/427) of atomoxetine subjects and 1.4% (4/294) placebo subjects discontinued for adverse events. For all studies, (including open-label and long-term studies), 5% of extensive metabolizer (EM) patients and 7% of poor metabolizer (PM) patients discontinued because of an adverse event. Among STRATTERA-treated patients, aggression (0.5%, N=2); irritability (0.5%, N=2); somnolence (0.5%, N=2); and vomiting (0.5%, N=2) were the reasons for discontinuation reported by more than 1 patient.

Commonly observed adverse events in acute child and adolescent, placebo-controlled trials—Commonly observed adverse events associated with the use of STRATTERA (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (STRATTERA incidence greater than placebo) are listed in Table 1 for the BID trials. Results were similar in the QD trial except as shown in Table 2, which shows both BID and QD results for selected adverse events. The most commonly observed adverse events in patients treated with STRATTERA (incidence of 5% or greater and at least twice the incidence in placebo patients, for either BID or QD dosing) were: dyspepsia, nausea, vomiting, fatigue, appetite decreased, dizziness, and mood swings (*see* Tables 1 *and* 2).

Table 1: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 9 weeks) Child and Adolescent Trials

Adverse Event[1]	Percentage of Patients Reporting Events from BID Trials	
	STRATTERA (N=340)	Placebo (N=207)
Gastrointestinal Disorders		
Abdominal pain upper	20	16
Constipation	3	1
Dyspepsia	4	2
Vomiting	11	9
Infections		
Ear infection	3	1
Influenza	3	1
Investigations		
Weight decreased	2	0
Metabolism and Nutritional Disorders		
Appetite decreased	14	6
Nervous System Disorders		
Dizziness (exc vertigo)	6	3
Headache	27	25
Somnolence	7	5
Psychiatric Disorders		
Crying	2	1
Irritability	8	5
Mood swings	2	0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	11	7
Rhinorrhea	4	3
Skin and Subcutaneous Tissue Disorders		
Dermatitis	4	1

[1] Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: anorexia, blood pressure increased, early morning awakening, flushing, mydriasis, sinus tachycardia, tearfulness. The following events were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: arthralgia, gastroenteritis viral, insomnia, sore throat, nasal congestion, nasopharyngitis, pruritus, sinus congestion, upper respiratory tract infection.

[See table 2 below]

The following adverse events occurred in at least 2% of PM patients and were either twice as frequent or statistically significantly more frequent in PM patients compared with EM patients: decreased appetite (23% of PMs, 16% of EMs); insomnia (13% of PMs, 7% of EMs); sedation (4% of PMs, 2% of EMs); depression (6% of PMs, 2% of EMs); tremor (4% of PMs, 1% of EMs); early morning awakening (3% of PMs, 1% of EMs); pruritus (2% of PMs, 1% of EMs); mydriasis (2% of PMs, 1% of EMs).

Adult Clinical Trials

Reasons for discontinuation of treatment due to adverse events in acute adult placebo-controlled trials—In the acute adult placebo-controlled trials, 8.5% (23/270) atomoxetine subjects and 3.4% (9/266) placebo subjects discontinued for

Table 2: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 9 weeks) Child and Adolescent Trials

Adverse Event	Percentage of Patients Reporting Events from BID Trials		Percentage of Patients Reporting Events from QD Trials	
	STRATTERA (N=340)	Placebo (N=207)	STRATTERA (N=85)	Placebo (N=85)
Gastrointestinal Disorders				
Abdominal pain upper	20	16	16	9
Constipation	3	1	0	0
Diarrhea	3	6	4	1
Dry mouth	1	2	4	1
Dyspepsia	4	2	8	0
Nausea	7	8	12	2
Vomiting	11	9	15	1
General Disorders				
Fatigue	4	5	9	1
Psychiatric Disorders				
Mood swings	2	0	5	2

adverse events. Among STRATTERA-treated patients, insomnia (1.1%, N=3); chest pain (0.7%, N=2); palpitations (0.7%, N=2); and urinary retention (0.7%, N=2) were the reasons for discontinuation reported by more than 1 patient.

Commonly observed adverse events in acute adult placebo-controlled trials—Commonly observed adverse events associated with the use of STRATTERA (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (STRATTERA incidence greater than placebo) are listed in Table 3. The most commonly observed adverse events in patients treated with STRATTERA (incidence of 5% or greater and at least twice the incidence in placebo patients) were: constipation, dry mouth, nausea, appetite decreased, dizziness, insomnia, decreased libido, ejaculatory problems, impotence, urinary hesitation and/or urinary retention and/or difficulty in micturition, and dysmenorrhea (*see* Table 3).

Table 3: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 10 weeks) Adult Trials

Adverse Event[1]	Percentage of Patients Reporting Events	
System Organ Class/ Adverse Event	STRATTERA (N=269)	Placebo (N=263)
Cardiac Disorders		
Palpitations	4	1
Gastrointestinal Disorders		
Constipation	10	4
Dry mouth	21	6
Dyspepsia	6	4
Flatulence	2	1
Nausea	12	5
General Disorders and Administration Site Conditions		
Fatigue and/or lethargy	7	4
Pyrexia	3	2
Rigors	3	1
Infections		
Sinusitis	6	4
Investigations		
Weight decreased	2	1
Metabolism and Nutritional Disorders		
Appetite decreased	10	3
Musculoskeletal, Connective Tissue, and Bone Disorders		
Myalgia	3	2
Nervous System Disorders		
Dizziness	6	2
Headache	17	17
Insomnia and/or middle insomnia	16	8
Paraesthesia	4	2
Sinus headache	3	1
Psychiatric Disorders		
Abnormal dreams	4	3
Libido decreased	6	2
Sleep disorder	4	2
Renal and Urinary Disorders		
Urinary hesitation and/or urinary retention and/or difficulty in micturition	8	0
Reproductive System and Breast Disorders		
Dysmenorrhea[3]	7	3
Ejaculation failure[2] and/or ejaculation disorder[2]	5	2
Erectile disturbance[2]	7	1
Impotence[2]	3	0
Menses delayed[3]	2	1
Menstrual disorder[3]	3	2
Menstruation irregular[3]	2	0
Orgasm abnormal	2	1
Prostatitis[2]	3	0
Skin and Subcutaneous Tissue Disorders		
Dermatitis	2	1
Sweating increased	4	1
Vascular Disorders		
Hot flushes	3	1

[1] Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: early morning awakening, peripheral coldness, tachycardia. The following events were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: abdominal pain upper, arthralgia, back pain, cough, diarrhea, influenza, irritability, nasopharyngitis, sore throat, upper respiratory tract infection, vomiting.

[2] Based on total number of males (STRATTERA, N=174; placebo, N=172).

[3] Based on total number of females (STRATTERA, N=95; placebo, N=91).

Male and female sexual dysfunction—Atomoxetine appears to impair sexual function in some patients. Changes in sexual desire, sexual performance, and sexual satisfaction are not well assessed in most clinical trials because they need special attention and because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate the actual incidence. The table below displays the incidence of sexual side effects reported by at least 2% of adult patients taking STRATTERA in placebo-controlled trials.

Table 4

	STRATTERA	Placebo
Erectile disturbance[1]	7%	1%
Impotence[1]	3%	0%
Orgasm abnormal	2%	1%

[1] Males only.

There are no adequate and well-controlled studies examining sexual dysfunction with STRATTERA treatment. While it is difficult to know the precise risk of sexual dysfunction associated with the use of STRATTERA, physicians should routinely inquire about such possible side effects.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

STRATTERA is not a controlled substance.

Physical and Psychological Dependence

In a randomized, double-blind, placebo-controlled, abuse-potential study in adults comparing effects of STRATTERA and placebo, STRATTERA was not associated with a pattern of response that suggested stimulant or euphoriant properties.

Clinical study data in over 2000 children, adolescents, and adults with ADHD and over 1200 adults with depression showed only isolated incidents of drug diversion or inappropriate self-administration associated with STRATTERA. There was no evidence of symptom rebound or adverse events suggesting a drug-discontinuation or withdrawal syndrome.

STRATTERA™ Capsules	10 mg*	18 mg*	25 mg*	40 mg*	60 mg*
Color	Opaque White, Opaque White	Gold, Opaque White	Opaque Blue, Opaque White	Opaque Blue, Opaque Blue	Opaque Blue, Gold
Identification	LILLY 3227 10 mg	LILLY 3238 18 mg	LILLY 3228 25 mg	LILLY 3229 40 mg	LILLY 3239 60 mg
NDC Codes:					
Bottles of 30	0002-3227-30	0002-3238-30	0002-3228-30	0002-3229-30	0002-3239-30

*Atomoxetine base equivalent.

Animal Experience

Drug discrimination studies in rats and monkeys showed inconsistent stimulus generalization between atomoxetine and cocaine.

OVERDOSAGE

The effects of overdose greater than twice the maximum recommended daily dose in humans are unknown.

No specific information is available on the treatment of overdose with atomoxetine. Patients who overdose with atomoxetine should be monitored carefully and receive supportive care. Gastric emptying and repeated activated charcoal (with/without cathartics) may prevent systemic absorption.

DOSAGE AND ADMINISTRATION

Initial Treatment

Dosing of children and adolescents up to 70 kg body weight—STRATTERA should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day (*see* CLINICAL STUDIES).

The total daily dose in children and adolescents should not exceed 1.4 mg/kg/day or 100 mg, whichever is less.

Dosing of children and adolescents over 70 kg body weight and adults—STRATTERA should be initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a target total daily dose of approximately 80 mg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. After 2 to 4 additional weeks, the dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response. There are no data that support increased effectiveness at higher doses (*see* CLINICAL STUDIES).

The maximum recommended total daily dose in children and adolescents over 70 kg and adults is 100 mg.

Maintenance/Extended Treatment

There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with STRATTERA. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use STRATTERA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

General Dosing Information

STRATTERA may be taken with or without food.

The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated.

Dosing adjustment for hepatically impaired patients—For those ADHD patients who have hepatic insufficiency (HI), dosage adjustment is recommended as follows: For patients with moderate HI (Child-Pugh Class B), initial and target doses should be reduced to 50% of the normal dose (for patients without HI). For patients with severe HI (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of normal (*see* Special Populations *under* CLINICAL PHARMACOLOGY).

Dosing adjustment for use with a strong CYP2D6 inhibitor—In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

Atomoxetine can be discontinued without being tapered.

HOW SUPPLIED

STRATTERA capsules are supplied in 10-, 18-, 25-, 40-, and 60-mg strengths.

[See first table above]

Continued on next page

Strattera—Cont.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)
[see USP Controlled Room Temperature].
Literature Revised March 5, 2003
PV 3752 AMP

INFORMATION FOR PATIENTS OR THEIR PARENTS OR CAREGIVERS

STRATTERA™
(atomoxetine HCl)

Read this information before you start taking STRATTERA (Stra-TAIR-a). Read this information you get each time you get more STRATTERA. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

What is STRATTERA?

STRATTERA is a non-stimulant medicine used to treat Attention-Deficit/Hyperactivity Disorder (ADHD). STRATTERA contains atomoxetine hydrochloride, a selective norepinephrine reuptake inhibitor. Your doctor has prescribed this medicine as part of an overall treatment plan to control your symptoms of ADHD.

What is ADHD?

ADHD has 3 main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all 3 types of symptoms.

Symptoms of ADHD in adults may include a lack of organization, problems starting tasks, impulsive actions, daydreaming, daytime drowsiness, slow processing of information, difficulty learning new things, irritability, lack of motivation, sensitivity to criticism, forgetfulness, low self-esteem, and excessive effort to maintain some organization. The symptoms shown by adults who primarily have attention problems but not hyperactivity have been commonly described as Attention-Deficit Disorder (ADD).

Many people have symptoms like these from time to time, but patients with ADHD have these symptoms more than others their age. Symptoms must be present for at least 6 months to be certain of the diagnosis.

Who should NOT take STRATTERA?

Do not take STRATTERA if:

- you took a medicine known as a monoamine oxidase inhibitor (MAOI) in the last 2 weeks. An MAOI is a medicine sometimes used for depression and other mental problems. Some names of MAOI medicines are Nardil® (phenelzine sulfate) and Parnate® (tranylcypromine sulfate). Taking STRATTERA with an MAOI could cause serious side effects or be life-threatening.
- you have narrow angle glaucoma, an eye disease.
- you are allergic to STRATTERA or any of its ingredients. The active ingredient is atomoxetine. The inactive ingredients are listed at the end of this leaflet.

What should I tell my doctor before taking STRATTERA?

Talk to your doctor before taking STRATTERA if you:

- have or had liver problems. You may need a lower dose.
- have high blood pressure. STRATTERA can increase blood pressure.
- have problems with your heart or an irregular heartbeat. STRATTERA can increase heart rate (pulse).
- have low blood pressure. STRATTERA can cause dizziness or fainting in people with low blood pressure.

Tell your doctor about all the medicines you take or plan to take, including prescription and non-prescription medicines, dietary supplements, and herbal remedies. Your doctor will decide if you can take STRATTERA with your other medicines.

Certain medicines may change the way your body reacts to STRATTERA. These include medicines used to treat depression [like Paxil® (paroxetine) and Prozac® (fluoxetine)], and certain other medicines (like quinidine). Your doctor may need to change your dose of STRATTERA if you are taking it with these medicines.

STRATTERA may change the way your body reacts to oral or intravenous albuterol (or drugs with similar actions), but the effectiveness of these drugs will not be changed. Talk with your doctor before taking STRATTERA if you are taking albuterol.

How should I take STRATTERA?

- Take STRATTERA according to your doctor's instructions. This is usually taken 1 or 2 times a day (morning and late afternoon/early evening).
- You can take STRATTERA with or without food.
- If you miss a dose, take it as soon as possible, but do not take more than your total daily dose in any 24-hour period.
- Taking STRATTERA at the same time each day may help you remember.
- STRATTERA is available in several dosage strengths: 10, 18, 25, 40, and 60 mg.

Call your doctor right away if you take more than your prescribed dose of STRATTERA.

Other important safety information about STRATTERA

Use caution when driving a car or operating heavy machinery until you know how STRATTERA affects you.

Talk to your doctor if you are:

- pregnant or planning to become pregnant
- breast-feeding. We do not know if STRATTERA can pass into your breast milk.

What are the possible side effects of STRATTERA?

The most common side effects of STRATTERA used in teenagers and children over 6 years old are:

- upset stomach
- decreased appetite
- nausea or vomiting
- dizziness
- tiredness
- mood swings

Weight loss may occur after starting STRATTERA. It is not known if growth will be slowed in children who use STRATTERA for a long period of time. Your doctor will watch your weight and height. If you are not growing or gaining weight as expected, your doctor may change your treatment of STRATTERA.

The most common side effects of STRATTERA used in adults are:

- constipation
- dry mouth
- nausea
- decreased appetite
- dizziness
- problems sleeping
- sexual side effects
- problems urinating
- menstrual cramps

Stop taking STRATTERA and call your doctor right away if you get swelling or hives. STRATTERA can cause a serious allergic reaction in rare cases.

This is not a complete list of side effects. Talk to your doctor if you develop any symptoms that concern you.

General advice about STRATTERA

STRATTERA has not been studied in children under 6 years old.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use STRATTERA for a condition for which it was not prescribed. Do not give STRATTERA to other people, even if they have the same symptoms you have.

This leaflet summarizes the most important information about STRATTERA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information on STRATTERA that is written for health professionals. You can also call 1-800-Lilly-Rx (1-800-545-5979) or visit our website at www.strattera.com.

What are the ingredients in STRATTERA?

Active ingredient: atomoxetine.

Inactive ingredients: pregelatinized starch, dimethicone, gelatin, sodium lauryl sulfate, FD&C Blue No. 2, synthetic yellow iron oxide, titanium dioxide, and edible black ink.

Store STRATTERA at room temperature.

This patient information summary has been approved by the US Food and Drug Administration.

Literature issued January 17, 2003
www.strattera.com
PV 3740 AMP

Shown in Product Identification Guide, page 322

VANCOCIN® HCl

℞

[*vān 'kō-sīn āch 'sē-ēl*]
(vancomycin hydrochloride capsules, USP)
Pulvules®

This preparation for the treatment of colitis is for oral use only and is not systemically absorbed. Vancocin® HCl must be given orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*. Orally administered Vancocin HCl is *not* effective for other types of infection. Parenteral administration of Vancocin HCl is not effective for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. If parenteral vancomycin therapy is desired, use Vancocin® HCl (Sterile Vancomycin Hydrochloride, USP), IntraVenous, and consult package insert accompanying that preparation.

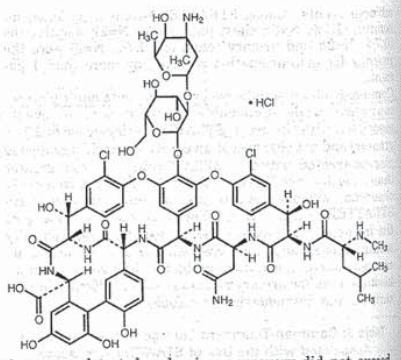
DESCRIPTION

Pulvules® Vancocin® HCl (Vancomycin Hydrochloride Capsules, USP) contain chromatographically purified vancomycin hydrochloride, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*), which has the chemical formula $C_{66}H_{75}Cl_2N_9O_{24}$•HCl. The molecular weight of vancomycin hydrochloride is 1,485.73; 500 mg of the base is equivalent to 0.34 mmol.

The Pulvules contain vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The Pulvules also contain F D & C Blue No. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredients.

Vancomycin hydrochloride has the following structural formula:

[See chemical structure at top of next column]



CLINICAL PHARMACOLOGY

Vancomycin is poorly absorbed after oral administration. During multiple dosing of 250 mg every 8 hours for 7 doses, fecal concentrations of vancomycin in volunteers exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%. Additional data using the oral solution dosage form follow. In anephric patients with no inflammatory bowel disease, blood concentrations of vancomycin were barely measurable (0.66 µg/mL) in 2 of 5 subjects who received 2 g of Vancocin HCl for Oral Solution daily for 16 days. No measurable blood concentrations were attained in the other 3 patients. With doses of 2 g daily, very high concentrations of drug can be found in the feces (>3,100 mg/kg) and very low concentrations (<1 µg/mL) can be found in the serum of patients with normal renal function who have pseudomembranous colitis. Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present. After multiple-dose oral administration of vancomycin, measurable serum concentrations may infrequently occur in patients with active *C. difficile*-induced pseudomembranous colitis, and, in the presence of renal impairment, the possibility of accumulation exists.

Microbiology—The bactericidal action of vancomycin results primarily from inhibition of cell-wall biosynthesis. In addition, vancomycin alters bacterial-cell-membrane permeability and RNA synthesis. There is no cross-resistance between vancomycin and other antibiotics.

NOTE: The oral form of vancomycin is effective only for the infections noted in the **INDICATIONS AND USAGE** section. The oral form is ***not*** effective for any other type of infection.

Vancomycin has been shown to be active against most strains of the following microorganisms in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Staphylococcus aureus (including methicillin-resistant strains) associated with enterocolitis

Anaerobic gram-positive microorganisms

Clostridium difficile antibiotic-associated pseudomembranous colitis

INDICATIONS AND USAGE

Vancocin HCl Pulvules may be administered orally for treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. Parenteral administration of Vancocin HCl is not effective for the above indications; therefore, Vancocin HCl must be given orally for these indications. **Orally administered Vancocin HCl is not effective for other types of infection.**

CONTRAINDICATION

Vancocin HCl is contraindicated in patients with known hypersensitivity to this antibiotic.

PRECAUTIONS

General—Clinically significant serum concentrations have been reported in some patients who have taken multiple oral doses of vancomycin for active *C. difficile*-induced pseudomembranous colitis; therefore, monitoring of serum concentrations may be appropriate in some instances, eg, in patients with renal insufficiency and/or colitis.

Some patients with inflammatory disorders of the intestinal mucosa may have significant systemic absorption of vancomycin and, therefore, may be at risk for the development of adverse reactions associated with the parenteral administration of vancomycin. (See package insert accompanying the intravenous preparation.) The risk is greater if renal impairment is present. It should be noted that the total systemic and renal clearances of vancomycin are reduced in the elderly.

Ototoxicity has occurred in patients receiving Vancocin HCl. It may be transient or permanent. It has been reported mostly in patients who have been given excessive intravenous doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Serial tests of auditory function may be helpful in order to minimize the risk of ototoxicity.

When patients with underlying renal dysfunction or those receiving concomitant therapy with an aminoglycoside are being treated, serial monitoring of renal function should be performed.

Use of vancomycin may result in the overgrowth of nonsusceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No long-term carcinogenesis studies in animals have been conducted.

Ultram—Cont.

fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing.

Labor and Delivery

ULTRAM should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn (see DRUG ABUSE AND DEPENDENCE). Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of ULTRAM, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers

ULTRAM is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied. Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

Pediatric Use

The safety and efficacy of ULTRAM in patients under 16 years of age have not been established. The use of ULTRAM in the pediatric population is not recommended.

Geriatric Use

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. In patients over 75 years of age, daily doses in excess of 300 mg are not recommended (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

A total of 455 elderly (65 years of age or older) subjects were exposed to ULTRAM in controlled clinical trials. Of those, 145 subjects were 75 years of age and older.

In studies including geriatric patients, treatment-limiting adverse events were higher in subjects over 75 years of age compared to those under 65 years of age. Specifically, 30% of those over 75 years of age had gastrointestinal treatment-limiting adverse events compared to 17% of those under 65 years of age. Constipation resulted in discontinuation of treatment in 10% of those over 75.

ADVERSE REACTIONS

ULTRAM was administered to 550 patients during the double-blind or open-label extension periods in U.S. studies of chronic nonmalignant pain. Of these patients, 375 were 65 years old or older. Table 2 reports the cumulative incidence rate of adverse reactions by 7, 30 and 90 days for the most frequent reactions (5% or more by 7 days). The most frequently reported events were in the central nervous system and gastrointestinal system. Although the reactions listed in the table are felt to be probably related to ULTRAM administration, the reported rates also include some events that may have been due to underlying disease or concomitant medication. The overall incidence rates of adverse experiences in these trials were similar for ULTRAM and the active control groups, TYLENOL® with Codeine #3 (acetaminophen 300 mg with codeine phosphate 30 mg), and aspirin 325 mg with codeine phosphate 30 mg, however, the rates of withdrawals due to adverse events appeared to be higher in the ULTRAM groups.

Table 2: Cumulative Incidence of Adverse Reactions for ULTRAM in Chronic Trials of Nonmalignant Pain (N = 427)

	Up to 7 Days	Up to 30 Days	Up to 90 Days
Diziness/Vertigo	26%	31%	33%
Nausea	24%	34%	40%
Constipation	24%	38%	46%
Headache	18%	26%	32%
Somnolence	16%	23%	25%
Vomiting	9%	13%	17%
Pruritus	8%	10%	11%
"CNS Stimulation"[1]	7%	11%	14%
Asthenia	6%	11%	12%
Sweating	6%	7%	9%
Dyspepsia	5%	9%	13%
Dry Mouth	5%	9%	10%
Diarrhea	5%	6%	10%

[1]"CNS Stimulation" is a composite of nervousness, anxiety, agitation, tremor, spasticity, euphoria, emotional lability and hallucinations.

Incidence 1% to less than 5%, possibly causally related: the following lists adverse reactions that occurred with an incidence of 1% to less than 5% in clinical trials, and for which the possibility of a causal relationship with ULTRAM exists.

Body as a Whole: Malaise.
Cardiovascular: Vasodilation.
Central Nervous System: Anxiety, Confusion, Coordination disturbance, Euphoria, Miosis, Nervousness, Sleep disorder.
Gastrointestinal: Abdominal pain, Anorexia, Flatulence.
Musculoskeletal: Hypertonia.
Skin: Rash.
Special Senses: Visual disturbance.
Urogenital: Menopausal symptoms, Urinary frequency, Urinary retention.

Incidence less than 1%, possibly causally related: the following lists adverse reactions that occurred with an incidence of less than 1% in clinical trials and/or reported in post-marketing experience.

Body as a Whole: Accidental injury, Allergic reaction, Anaphylaxis, Death, Suicidal tendency, Weight loss, Serotonin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma).
Cardiovascular: Orthostatic hypotension, Syncope, Tachycardia.
Central Nervous System: Abnormal gait, Amnesia, Cognitive dysfunction, Depression, Difficulty in concentration, Hallucinations, Paresthesia, Seizure (see WARNINGS), Tremor.
Respiratory: Dyspnea.
Skin: Stevens-Johnson syndrome/Toxic epidermal necrolysis, Urticaria, Vesicles.
Special Senses: Dysgeusia.
Urogenital: Dysuria, Menstrual disorder.

Other adverse experiences, causal relationship unknown: A variety of other adverse events were reported infrequently in patients taking ULTRAM during clinical trials and/or reported in post-marketing experience. A causal relationship between ULTRAM and these events has not been determined. However, the most significant events are listed below as alerting information to the physician.
Cardiovascular: Abnormal ECG, Hypertension, Hypotension, Myocardial ischemia, Palpitations, Pulmonary edema, Pulmonary embolism.
Central Nervous System: Migraine, Speech disorders.
Gastrointestinal: Gastrointestinal bleeding, Hepatitis, Stomatitis, Liver failure.
Laboratory Abnormalities: Creatinine increase, Elevated liver enzymes, Hemoglobin decrease, Proteinuria.
Sensory: Cataracts, Deafness, Tinnitus.

DRUG ABUSE AND DEPENDENCE

ULTRAM may induce psychic and physical dependence of the morphine-type (µ-opioid). (See WARNINGS.) Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. ULTRAM is associated with craving and tolerance development. Withdrawal symptoms may occur if ULTRAM is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

OVERDOSAGE

Serious potential consequences of overdosage are respiratory depression, lethargy, coma, seizure, cardiac arrest and death. (See WARNINGS.) Fatalities have been reported in post marketing in association with both intentional and unintentional overdose with ULTRAM. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. While naloxone will reverse some, but not all, symptoms caused by overdosage with ULTRAM, the risk of seizures is also increased with naloxone administration. In animals convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

DOSAGE AND ADMINISTRATION

Adults (17 years of age and over)

For patients with moderate to moderately severe chronic pain not requiring rapid onset of analgesic effect, the tolerability of ULTRAM can be improved by initiating therapy with the following titration regimen: ULTRAM should be started at 25 mg/day qAM and titrated in 25 mg increments as separate doses every 3 days to reach 100 mg/day (25 mg q.i.d.). Thereafter the total daily dose may be increased by 50 mg as tolerated every 3 days to reach 200 mg/day (50 mg q.i.d.). After titration, ULTRAM 50 to 100 mg can be administered as needed for pain relief every 4 to 6 hours **not to exceed 400 mg/day.**

For the subset of patients for whom rapid onset of analgesic effect is required and for whom the benefits outweigh the risk of discontinuation due to adverse events associated with higher initial doses, ULTRAM 50 mg to 100 mg can be administered as needed for pain relief every four to six hours, **not to exceed 400 mg per day.**

Individualization of Dose

Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Studies with tramadol in adults have shown that starting at the lowest possible dose and titrating upward will result in fewer discontinuations and increased tolerability.

- In all patients with **creatinine clearance less than 30 mL/min,** it is recommended that the dosing interval of ULTRAM be increased to 12 hours, with a maximum daily dose of 200 mg. Since only 7% of an administered dose is removed by hemodialysis, **dialysis patients** can receive their regular dose on the day of dialysis.
- The recommended dose for adult patients with **cirrhosis** is 50 mg every 12 hours.
- In general, dose selection for an elderly patient over 65 years old should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy. For elderly patients **over 75 years old,** total dose should not exceed 300 mg/day.

HOW SUPPLIED

ULTRAM (tramadol hydrochloride tablets) Tablets – 50 mg (white, scored, film-coated capsule-shaped tablet) debossed "ULTRAM" on one side and "06 59" on the other side.
100's – NDC 0045-0659-60 bottles of 100 tablets
500's – NDC 0045-0659-70 bottles of 500 tablets
Packages of 100 unit doses in blister packs – NDC 0045-0659-10 (10 cards of 10 tablets each).
Dispense in a tight container. Store at 25°C (77°F); excursions permitted to 15-30°C (59-89°F).

ORTHO-McNEIL
OMP DIVISION
ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey 08869
U.S. Patents 3,652,589 and 3,830,934
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Shown in Product Identification Guide, page 330

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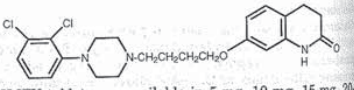
ABILIFY™ ℞

[ă-bĭl-ĭfī]
(aripiprazole) Tablets
℞ only

DESCRIPTION

ABILIFY™ (aripiprazole) is a psychotropic drug that is available as tablets for oral administration. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The chemical structure is:



ABILIFY tablets are available in 5-mg, 10-mg, 15-mg, 20-mg, and 30-mg strengths. Inactive ingredients include lactose monohydrate, cornstarch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic and histamine H_1 receptors (K_i values of 44, 15, 39, 57, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K_i=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50} >1000 nM). Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor.

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole, e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha$_1$ receptors.

Pharmacokinetics

ABILIFY activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major me-

tabolite, dehydro-aripiprazole, which has been shown to have affinities for D_2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

Absorption

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. ABILIFY can be administered with or without food. Administration of a 15-mg ABILIFY tablet with a standard high-fat meal did not significantly affect the C_{max} or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed T_{max} by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent D_2-receptor occupancy indicating brain penetration of aripiprazole in humans.

Metabolism and Elimination

Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Coadministration of ABILIFY (aripiprazole) with known inhibitors of CYP2D6, like quinidine in EMs, results in a 112% increase in aripiprazole plasma exposure, and dosing adjustment is needed (see **PRECAUTIONS: Drug-Drug Interactions**). The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs, respectively. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Following a single oral dose of [^{14}C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

Special Populations

In general, no dosage adjustment for ABILIFY is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function (see **DOSAGE AND ADMINISTRATION: Dosage in Special Populations**). The pharmacokinetics of aripiprazole in special populations are described below.

Hepatic Impairment

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

Renal Impairment

In patients with severe renal impairment (creatinine clearance <30 mL/min), C_{max} of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

Elderly

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients (see **PRECAUTIONS: Geriatric Use**).

Gender

C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

Smoking

Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

Drug-Drug Interactions

Potential for Other Drugs to Affect ABILIFY (aripiprazole)

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.

Potential for ABILIFY (aripiprazole) to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **PRECAUTIONS: Drug-Drug Interactions**).

Aripiprazole had no clinically important interactions with the following drugs:

Famotidine: Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40-mg single dose of the H_2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the C_{max} of aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

Valproate: When valproate (500–1500 mg/day) and aripiprazole (30 mg/day) were coadministered at steady state, the C_{max} and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

Lithium: A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200–1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C_{max} and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

Dextromethorphan: Aripiprazole at doses of 10 to 30 mg per day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway known to be dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methyoxymorphan, a pathway known to be dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole.

Warfarin: Aripiprazole 10 mg per day for 14 days had no effect on the pharmacokinetics of R- and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

Omeprazole: Aripiprazole 10 mg per day for 15 days had no effect on the pharmacokinetics of a single 20-mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with aripiprazole.

Clinical Studies

The efficacy of ABILIFY (aripiprazole) in the treatment of schizophrenia was evaluated in four short-term (4- and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Three of the four trials were able to distinguish aripiprazole from placebo, but one study, the smallest, did not. Three of these studies also included an active control group consisting of either risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for a comparison of ABILIFY and the active comparators.

In the three positive trials for ABILIFY, four primary measures were used for assessing psychiatric signs and symptoms. The Positive and Negative Syndrome Scale (PANSS) is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. The PANSS positive subscale is a subset of items in the PANSS that rates seven positive symptoms of schizophrenia (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility). The PANSS negative subscale is a subset of items in the PANSS that rates seven negative symptoms of schizophrenia (blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, stereotyped thinking). The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n=414) comparing two fixed doses of ABILIFY (15 or 30 mg/day) and haloperidol (10 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, and CGI-severity score. In addition, the 15-mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n=404) comparing two fixed doses of ABILIFY (20 or 30 mg/day) and risperidone (6 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of ABILIFY (10, 15, or 20 mg/day) to placebo, all three doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, and the PANSS negative subscale.

In a fourth study, a 4-week trial (n=103) comparing ABILIFY in a range of 5 to 30 mg/day or haloperidol 5 to 20 mg/day to placebo, haloperidol was superior to placebo, in the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis, and in a responder analysis based on the CGI-severity score, the primary outcomes for that trial. ABILIFY was only significantly different compared to placebo in a responder analysis based on the CGI-severity score.

Thus, the efficacy of 15-mg, 20-mg, and 30-mg daily doses was established in two studies for each dose, whereas the efficacy of the 10-mg dose was established in one study. There was no evidence in any study that the higher dose groups offered any advantage over the lowest dose group.

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

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 creatinine 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.

Continued on next page

Abilify—Cont.

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.

PRECAUTIONS

General

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY (aripiprazole) included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%); orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of 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 (aripiprazole) 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 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 discuss the following issues with patients for whom they prescribe ABILIFY (aripiprazole):

Interference with Cognitive and Motor Performance

Because aripiprazole may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely.

Pregnancy

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

Nursing

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

Concomitant Medication

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

Alcohol

Patients should be advised to avoid alcohol while taking ABILIFY.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Drug-Drug Interactions

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY (aripiprazole) 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 (aripiprazole).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2).

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

Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was

obtained in the *in vivo* micronucleus assay in mice, however, the response was shown to be due to a mechanism not considered relevant to humans.

Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m^2 basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

Pregnancy

Pregnancy Category C

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

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

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

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

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

Labor and Delivery

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

Of the 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 pharmakinetics 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 (aripiprazole) in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 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 exposure. A total of 1887 aripiprazole-treated patients were treated for at least 180 days and 1251 aripiprazole-treated patients had at least 1 year of exposure.

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

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; ie, all reported events are included.

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

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

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

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

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

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

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks), 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.

Table 1: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials

Body System Adverse Event	Percentage of Patients Reporting Event[a] Aripiprazole (n=926)	Placebo (n=413)
Body as a Whole		
Headache	32	25
Asthenia	7	5
Fever	2	1
Digestive System		
Nausea	14	10
Vomiting	12	7
Constipation	10	8
Nervous System		
Anxiety	25	24
Insomnia	24	19
Lightheadedness	11	7
Somnolence	11	8
Akathisia	10	7
Tremor	3	2
Respiratory System		
Rhinitis	4	3
Coughing	3	2
Skin and Appendages		
Rash	6	5
Special Senses		
Blurred vision	3	1

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

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

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials 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, 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 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.

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%)]. The following table 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 2: Weight Change Results Categorized by BMI at Baseline

	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 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.

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 5592 patients. All reported events are included except those already listed in Table 1, or other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of <0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

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

Body as a Whole: Frequent – flu syndrome, 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.

Continued on next page

Abilify—Cont.

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, blunted 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, pruritis, sweating, skin ulcer; *Infrequent* – acne, vesiculobullous rash, eczema, alopecia, psoriasis, seborrhea; *Rare* – maculopapular rash, exfoliative dermatitis, urticaria.
Special Senses: Frequent – conjunctivitus, 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.

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

Human Experience
In premarketing clinical studies, involving more than 5500 patients, accidental or intentional acute overdosage of aripiprazole was identified in seven patients. In the two patients taking the largest identified amount, 180 mg, the only symptoms reported were somnolence and vomiting in one of the two patients. In the patients who were evaluated in hospital settings, including the two patients taking 180 mg, there were no observations indicating an adverse change in vital signs, laboratory assessments, or ECG. An uneventful, accidental overdose (15 mg) occurred in a non-patient, an 18-month-old child, with concomitant ingestion of ATIVAN® (2 mg).
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 (aripiprazole), 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.

DOSAGE AND ADMINISTRATION

Usual Dose
The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day; however, doses higher than 10 or 15 mg/day, the lowest doses in these trials, were not more effective than 10 or 15 mg/day. Dosage increases should not be made before 2 weeks, the time needed to achieve steady state.
Dosage in Special Populations
Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status (see **CLINICAL PHARMACOLOGY: Special Populations**).
Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP3A4 inhibitors: When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.
Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP2D6 inhibitors: When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

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Dosage adjustment for patients taking potential CYP3A4 inducers: When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be doubled (to 20 to 30 mg). Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 to 15 mg.
Maintenance Therapy
There is no body of evidence available from controlled trials to answer the question of how long a patient treated with aripiprazole should remain on it. It is generally agreed, however, that pharmacological treatment for episodes of acute schizophrenia should continue for up to 6 months or longer. Patients should be periodically reassessed to determine the need for maintenance treatment.
Switching from Other Antipsychotics
There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

ANIMAL TOXICOLOGY

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40- and 60-mg/kg doses represent 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m^2 and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

HOW SUPPLIED

ABILIFY™ (aripiprazole) Tablets are available in the following strengths and packages.

The 5-mg ABILIFY tablets are blue, modified rectangular tablets, debossed on one side with "A-007" and "5".
Bottles of 30 NDC 59148-007-13
Blister of 100 NDC 59148-007-35
The 10-mg ABILIFY tablets are pink, modified rectangular tablets, debossed on one side with "A-008" and "10".
Bottles of 30 NDC 59148-008-13
Blister of 100 NDC 59148-008-35
The 15-mg ABILIFY tablets are yellow, round tablets, debossed on one side with "A-009" and "15".
Bottles of 30 NDC 59148-009-13
Blister of 100 NDC 59148-009-35
The 20-mg ABILIFY tablets are white, round tablets, debossed on one side with "A-010" and "20".
Bottles of 30 NDC 59148-010-13
Blister of 100 NDC 59148-010-35
The 30-mg ABILIFY tablets are pink, round tablets, debossed on one side with "A-011" and "30".
Bottles of 30 NDC 59148-011-13
Blister of 100 NDC 59148-011-35

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 Co, Princeton, NJ 08543 USA
Manufactured by Otsuka Pharmaceutical Co, Ltd, Tokyo, 101-8535 Japan
Distributed by Bristol-Myers Squibb Co, Princeton, NJ 08543 USA
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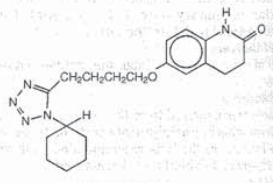
[PLAY-tal]
(cilostazol) (sil-OS-tah-zol)
Tablets

CONTRAINDICATION
Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharmacologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive heart failure. PLETAL is contraindicated in patients with congestive heart failure of any severity.

DESCRIPTION

PLETAL (cilostazol) is a quinolinone derivative that inhibits cellular phosphodiesterase (more specific for phosphodiesterase III). The empirical formula of cilostazol is $C_{20}H_{27}N_5O_2$, and its molecular weight is 369.47. Cilostazol is 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl)butoxyl-3,4-dihydro-2(1*H*)-quinolinone, CAS-73963-72-1.
The structural formula is:



CILOSTAZOL

Cilostazol occurs as white to off-white crystals or as a crystalline powder that is slightly soluble in methanol and ethanol, and is practically insoluble in water, 0.1 N HCl, and 0.1 N NaOH.
PLETAL (cilostazol) tablets for oral administration are available in 50 mg triangular and 100 mg round, white debossed tablets. Each tablet, in addition to the active ingredient, contains the following inactive ingredients: carboxymethylcellulose calcium, corn starch, hydroxypropyl methylcellulose 2910, magnesium stearate, and microcrystalline cellulose.

CLINICAL PHARMACOLOGY

Mechanism of Action:
The mechanism of the effects of PLETAL on the symptoms of intermittent claudication is not fully understood. PLETAL and several of its metabolites are cyclic AMP (cAMP) phosphodiesterase III inhibitors (PDE III inhibitors), inhibiting phosphodiesterase activity and suppressing cAMP degradation with a resultant increase in cAMP in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation, respectively.
PLETAL reversibly inhibits platelet aggregation induced by a variety of stimuli, including thrombin, ADP, collagen, arachidonic acid, epinephrine, and shear stress. Effects on cir-