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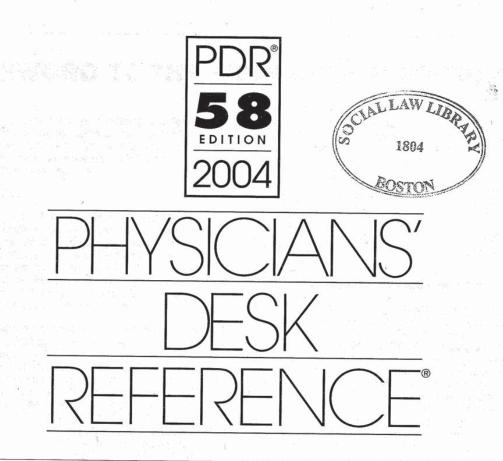
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FOREWORD TO THE FIFTY-EIGHTH EDITION

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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. newbs tanked 000.5 to does now be

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 warability chaotien allovia yellt to somern for Internacions Schwem as many et 32 drogs The What's New reature

rant 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 decisionwith 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. Entered and because to exist a second

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 FDAapproved dosing recommendations for more than 1,500 drugs. Unlike other condensed drug references, the information is drawn almost exclusively from the FDAapproved 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-thecounter 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 GuideTM**, 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 Windowscompatible 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*TM — 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.

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Manufacturers' Index (White Pages)

Section 1

Lists all pharmaceutical manufacturers participating in PHYSICIANS' DESK REFERENCE. Includes addresses, phone numbers, and emergency contacts. Shows each manufacturer's products and the page number of those described in PDR.

Brand and Generic Name Index (Pink Pages) 101

Section 2

Gives the page number of each product by brand and generic name.

Product Category Index (Blue Pages)	201

Section 3

Lists all fully described products by prescribing category. An overview of the headings appears on pages 201 and 202.

Product Identification Guide (Gray Pages)

Section 4

Presents full-color, actual-size photos of tablets and capsules, plus pictures of a variety of other dosage forms and packages. Arranged alphabetically by manufacturer.

Product Information (White Pages)

Section 5

The main section of the book. Includes entries for some 3,000 pharmaceuticals. Listings are arranged alphabetically by manufacturer.

Diagnostic Product Information

3535 Section 6 Gives usage guidelines for a variety of diagnostic agents. Arranged alphabetically by manufacturer. Provides a listing of drugs arranged by pregnancy category. Includes basic patient instructions and pronunciations. Gives the definition of each category and the prescribing limitations that apply. Provides at-a-glance description of each risk/benefit rating. Poison Control Centers A national directory arranged alphabetically by state and city. A national directory arranged alphabetically by state and city. Gives numbers of key reporting programs and information services. Gives numbers of U.S. divisions and office locations.

Provides contact information arranged alphabetically by state. Adverse Event Report Forms Includes master copies and instructions for completion.

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 name		
Indicates photo	 INDOCIN SUPPOSITORIES (Merck)	
Generic name		Manufacturer
	Indocin Capsules (Merck)	Bold page number
	Indocin Oral Suspension (Merck)2000	indicates complete prescribing information
Brands of indomethacin	Indocin Suppositories (Merck)	
	(Mylan)	

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.

SECTION 2

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*™.

A set of the set of th	Lastah 10/500 Tehlas (UCD) 2025		and a second of
A	Lortab 10/500 Tablets (UCB)	Maximum Strength Tylenot Sore Throat Adult Liquid (McNeil	Propoxyphen Acetamino
ABACAVIR SULFATE	Maxidone Tablets CIII (Watson)	Consumer)	Propoxyphen
Trizivir Tablets	Midrin Capsules (Women First) 3396	Tylenol with Codeine Elixir	Acetamino
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(GlaxoSmithKline)	Norco 10/325 Tablets CIII (Watson) 3361	(Ortho-McNeil)	(Mallinckri
Ziagen Tablets	Percocet Tablets (Endo Labs)	Women's Tylenol Menstrual Relief Caplets (McNeil	Propoxyphene
(GlaxoSmithKline)	Sedapap Tablets 50 mg/650 mg (Merz) 2126	Consumer)	Roxicet Oral
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SOLUTION (Dey). 312, 1194	Concentrated Tylenol Infants'	(Pharmaceutical Associates) 2701 Acetaminophen and Codeine	ACITRETIN
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and the second se	(McNeil Consumer)	Anexsia Tablets (Mallinckrodt)	ACLOVATE C
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CUTANE CAPSULES	Consumer)	Butalbital, Acetaminophen, Caffeine,	(GlaxoSmith
(Roche Laboratories)	Extra Strength Tylenol Gelcaps,	and Codeine Phosphate Capsules	ACRIVASTIN
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Caplets and Geltabs (Bristol	Maximum Strength Tylenol Sinus Night Time Caplets	Oxycodone and Acetaminophen	ACULAR PF
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⊙ Described in PDR For Ophthalmic Medicines™

GoLytely/NuLytely-Cont.

Each jug contains: NuLYTELY: polyethylene glycol 3350 420 g, sodium bicarbo-nate 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 chlo-ride 1.48 g and flavoring ingredients 2.0 g. When made up to 4 liters volume with water, the solution contains PEG-3350

4 liters volume with water, the solution contains PEG-3350 31.3 mmol/L, sodium 65 mmol/L, chloride 53 mmol/L, bicar-bonate 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, chlo-ride 53 mmol/L bicarbonate 17 mmol/L and textures. ride 53 mmol/L, bicarbonate 17 mmol/L and potassium 5 mmol/T

5 mmol/L. Orange NuLYTELY: polyethylene glycol 3350 420 g, sodium bicarbonate 5.72 g, sodium chloride 11.2 g, potassium chlo-ride 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, bicar-bonete 17 mmol/L and heterseine 55 mmol/L bicar-bonete 17 mmol/L bicar-bonete 17 mmol/L bicar-bonete 17 bonate 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 'lar]

Polyethylene Glycol 3350, NF Powder for Solution Full Prescribing Information

DESCRIPTION

DESCRIPTION A white powder for reconstitution. MiraLax (polyethylene glycol 3350, NF powder for solution) is a synthetic polygly-col 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 chem-ical formula is $\mathrm{HO}(\mathrm{C}_{\mathrm{sH}}(\mathbf{0})_{\mathrm{sH}}$ in which n represents the av-erage 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 rewater to be retained with the stool. Essentially, complete re-covery of MiraLax was shown in normal subjects without constipation. Attempts at recovery of MiraLax in consti-pated 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 mi-croflora in human feces. MiraLax appears to have no effect on the active absorption or secretion of glucose or electro-lytes. There is no suidence of tochymelynoin. lytes. 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 ob-served for both treatment groups during the first week of treatment. MiraLax was statistically superior to placebo during the competence of the first week of the second 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 anothing to use every of intratate of proceed in the days each. Success was defined by an increase in both bowel movement frequency and daily stool weight. For both pa rameters, 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.

Information will be superseded by supplements and subsequent editions

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 adequate dietary fiber and fluid intake, regular exercise) which may produce more regular bowel habits.

MiraLax should be administered after being dissolved in ap-proximately 8 ounces of water, juice, soda, coffee, or tea. Information for Patients: MiraLax softens the stool and in-

creases the frequency of bowel movements by retaining wa-ter 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. 4 days may be required to produce a bowel move-

ment. 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 labo-

ratory 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, genetic toxicity studies and re-productive toxicity studies in animals have not been per-formed 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 pa-tients has not been established.

Geriatric Use: There is no evidence for special consider-ations when MiraLax is administered to elderly patients. In geriatric nursing home patients a higher incidence of di-arrhea occurred at the recommended 17 gram dose. If diar-rhea 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

R

There have been no reports of accidental overdosage. In the There have been no reports of accidential 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 adminis-tered. 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 The usual dose is 1/ grams (about 1 neaping tablespoin) or 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 lax-ative 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 m Temperature

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

Shown in Product Identification Guide, page 310

PHYSICIANS' DESK REFERENCE®

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 & AM-5:00 PM EST: (800) 631-5244

Mailing your purchase orders to:

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Princeton, NJ 08543-5250

Faxing your purchase orders to: (800) 523-2965 Transmitting computer-to-computer on the NWDA and

UCS formats through Ordernet Services DEA#PE0048579

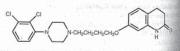
R

ABILIFY [ă-bil-ifi]

(aripiprazole) Tablets only

DESCRIPTION

ABILIFYTM (aripiprazole) is a psychotropic drug that is available as tablets for oral administration. Aripiprazole s 7-[4-[4-(2,3-dichlorophenyl])-1-piperazinyl]butoxyl 3,4-dia drocarbostyril. The empirical formula is $C_{22}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The chemical struct



ABILIFY tablets are available in 5-mg, 10-mg, 15-mg, mg, and 30-mg strengths. Inactive ingredients inclusion tose monohydrate, cornstarch, microcrystalline cellux, hydroxypropyl cellulose, and magnesium stearate. Chr rants include ferric oxide (yellow or red) and FD&C Ex No. 2 Aluminum Lake.

CLINICAL PHARMACOLOGY

Characteristics of the second pamine D₄, serotonin 5-HT_{2C} and 5-HT₇, alpha₁-adreners and histamine H₁ receptors (K_i values of 44, 15, 39, 57, ad and instamle 14, 10, 53, 57, and 61 M, respectively), and moderate affinity for the serven reuptake site (K₂=98 nM). Aripiprazole has no apprecial affinity for cholinergic muscarinic receptors (\mathbb{I}_{9} >1000 nM). Aripiprazole functions as a partial agonts i the dopamine D₂ and the serven as a partial agonts i an antagenetic to conclusion \mathbb{E} HT has the server of the server o

The uppainting D_2 and the serotomic $D_1 H_{1,1}$ receptors, and an antagonist at serotomic $D_1 H_{2,1}$ receptor. The mechanism of action of aripiprazole, as with during having efficacy in schizophrenia, is unknown. Here, the been proposed that the efficacy of aripiprazies mediated through a combination of partial agonist activity $D_1 = D_2$ and D_2 and D_2 and D_3 and mediated through a combination of partial agonsis atom at D₂ and 5-HT₁_A receptors and antagonist atom 5-HT_{2A} receptors. Actions at receptors other than D₅-5-HT_{2A} may explain some of the other dimin effects of arippirazole, e.g., the orthostatic hypotension to served with aripiprazole may be explained by its antagons

served with arbitrazole may be explained by its anagons activity at adrenergic alpha₁ receptors. **Pharmacokinetics** ABILIFY activity is presumably primarily due to the para drug, arbitrazole, and to a lesser extent, to its may re-tabolite, dehydro-aripiprazole, which has been shown is have affinities for D_2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasm The mean expresents 40% of the parent drug exposure in piscal The mean elimination half-lives are about 75 hours and 8 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole are mulation is predictable from single-dose pharmacokinets. At steady state, the pharmacokinetics of aripiprazole is dose-proportional. Elimination of aripiprazole is many through hepatic metabolism involving two P450 isozyms OVDDC = 1 OVDDA CYP2D6 and CYP3A4.

Absorption

D 6/01

Arsipprazole is well absorbed, with peak plasma concentrions occurring within 3 to 5 hours; the absolute onl be availability of the tablet formulation is 87%. ABILIFY as be administered with or without food. Administration of 15-mg ABILIFY tablet with a standard high-fat med at not significantly affect the Cmax or AUC of aripiprazole at the

> Roxane Labs., Inc. Exhibit 1008 Page 011

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

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

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 49 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 D₂-receptor occupancy indicating brain penteration of aripiprazole in humans. Metabolism and Elimination

Aripprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and Ndealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyed by CYP34A. Aripiprazole is the predominant drug maety in the systemic circulation. At steady state, dehydroampiprazole, the active metabolite, represents about 40% of ampiprazole. dUC in plasma.

approximately 8% of Caucasians lack the capacity to meabolize CYP2D6 substrates and are classified as poor meabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole erposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% injete exposure to the total active moieties from a given des of anpiprazole compared to EMs. Coadministration of RELIFY (aripiprazole) with known inhibitors of CYP2D6, ine quindine in EMs, results in a 112% increase in aripprazole plasma exposure, and dosing adjustment is needed use PRECAUTIONS: Drug-Drug Interactions). The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole with Ns, respectively. Aripiprazole des no inhibit or induce the CYP2D6 pathway.

Pallowing a single oral dose of [¹⁴C]-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 undanged in the feces.

pecial Populations

In genral, no dosage adjustment for ABILIFY is required an theosis of a patient's age, gender, race, smoking status, basic function, or renal function (see DOSAGE AND AD-MINISTRATION: Dosage in Special Populations). The pharmaokinetics of aripiprazole in special populations are accrited below.

Hepatic Impairment

has single-does 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 edgets, increased 31% in midd H1, increased 8% in moderate H and decreased 20% in severe HI. None of these difiences would require dose adjustment.

Renal Impairment

In patients with severe renal impairment (creatinine clearane <0 mL/min), C_{musi} of aripiprazole (given in a single dese of 15 mg) and dehydro-aripiprazole increased by 36% ad 337, respectively, but AUC was 15% lower for aripipranele and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripipraade is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

In formal single-dose pharmacokinetic studies (with aripprzade given in a single dose of 15 mg), aripiprazole clearnet 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 pharmamokinetic analysis in schizophrenia patients. Also, the pharmachinetic analysis in schizophrenia patients. Also, the pharmachinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, bathy subjects. No dosage adjustment is recommended for elderly patients (see **PRECAUTIONS: Geriatric Use**).

 $G_{\rm ex}$ and AUC of aripiprazole and its active metabolite, denote aripiprazole, are 30 to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommeded based on gender.

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

moking

Rans

Based on studies utilizing human liver enzymes in vitro, amprazole 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 pharmaokinetic evaluation did not reveal any significant pharmaokinetic 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 exymes. 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.

aprazole with initiators of 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., ketconazole) 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 **PRECAU-TIONS: Drug-Drug Interactions**).

Aripiprazole had no clinically important interactions with the following drugs:

the following drugs: Famotidine: Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40-mg single dose of the H₂ 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 15%, respectively, and by 13% and 15%, respectively, and 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 (300 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole ($C_{\rm max}$ 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 Odealkylation 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 aripinprazole.

dosage adjustment of dextinethorphan 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 CYP2C19 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

binding of highly protein-bound warrarin. 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-IIL/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 meas-

In the three positive trials for ADLLP , four primary measures were used for assessing syschiatric 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 bositive 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). Iack 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 CGIseverity 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

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 CLINI-CAL 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

Consult 2004 PDR[®] supplements and future editions for revisions

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 with-drawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the under-lying process. The effect that symptomatic suppression has

Jung protess reconcerned of physical supports 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 ap-propriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment pro-ducing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed

The need for continued streaments periodically. If signs and symptoms of tardive dyskinesia appear in a pa-tient on ABILIFY, drug discontinuation should be consid-ered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

PRECAUTIONS

General Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α 1-adrenergic receptor antago nism. The incidence of orthostatic hypotension associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY (aripiprazole) included: schuzophreina (1920) of holinar i (anpipazole) included, orthostatic lightheadedness (placebo 1%, aripiprazole 1.9%) or thostatic lightheadedness (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 arip-iprazole 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 re-ported 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 pla-cebo, ABILIFY, like other antipsychotics, may have the po-CEOD, ADLLT, , like other antipsycholics, may have the po-tential to impair judgment, thinking, or motor skills. Pa-tients 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

Doiry temperature regulation Disruption of the body's ability to reduce core body temper-ature has been attributed to antipsychotic agents. Appropri-ate care is advised when prescribing aripiprazole for pa-tients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., ex-ercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Esophageal dysmotility and aspiration have been associated Esophageal dysmouthy and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly-pa-tients, in particular those with advanced Alzheimer's de-mentia. 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 Associ-ated with Alzheimer's Disease:

Information will be superseded by supplements and subsequent editions

In a flexible dose (2 to 15 mg/day), 10-week, placebo-controlled study of aripiprazole in elderly patients (mean controlled study of arripprazole in elderly patients (mean age: 81.5 years; range: 56 to 95 years) with psychosis asso-ciated 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 follow-ing the discontinuation of ABILIFY in the double-blind ing 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 25% 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, ascend-ing-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 pa-

The statety and elineacy of ADLIFT in the treatment of pa-tients with psychosis associated with dementia have not been established. If the prescriber elects to treat such pa-tients with ABILIFY, vigilance should be exercised, partic-ularly for the emergence of difficulty swallowing or exces-sive somnolence, which could predispose to accidental injury or aspiration. Clinical experience with ABILIFY in patients with certain

concomitant systemic illnesses (see CLINICAL PHARMA-COLOGY: 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 in-farction or unstable heart disease. Patients with these diag-noses 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 judg-ment, thinking, or motor skills, patients should be cau-tioned about operating hazardous machinery, including automobiles, until they are reasonably certain aripiprazole therapy does not affect them adversely. certain that Pregnancy

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

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-t counter drugs, since there is a potential for interactions on or over-the

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

Heat Exposure and Dehydration Patients should be advised regarding appropriate care in rations 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 antihyperagents. tensive

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

both CFF DAY and CFF 2DO are responsible for an ppractice metabolism. Agents that induce CYP3A4 (e.g., carbanaze-pine) could cause an increase in arripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) cor CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

Ketoconazole: Coadministration of ketoconazole (200 mg Account of a contract of the comitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its occurs, an inprazine does should be reduced to one-hall of its normal does. Other strong inhibitors of CYP3A4 (ifracon-zole) 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, arip-

inhibitor is withdrawn from the combination therapy, arip-iprazole dose should then be increased. *Quinidine:* Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a po-tent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of states are tabolite, de-hydro-aripiprazole, by 35%. Aripiprazole dose should be re-duced to one-half of its normal dose when concomitant ad-ministration of our primerable accure. Other ministration 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 too mg QD resided in an approximate 10% decrease in $C_{\rm max}$ and AUC values of both aripiprazole and its active me-tabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clin-ical 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 cyto-chrome 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), OY CYP2CI9 (omeprazole, warfarin), and CYP3A4 (dextro-methorphan) 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 arip-iprazole 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 al-cohol 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. Aripipra-zole 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/ To, and so marginary to first mice and 1, 5, 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/m², re-spectively). 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/m²). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pitu-itary 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/m²). In female rats, the incidence of mammary gland on mg/m). In remark rats, the incidence of mammary grand 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/m²); 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/m²).

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 prolactinmediated 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 DIA's patternal reverse-mutation assay, the in vitro bacternal DNA repair assay, the in vitro forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberra-tion 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 aber-ration 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 con-sidered 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 hu-man dose [MRHD] on a mg/m² 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.

PRODUCT INFORMATION

Pregnancy

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

Pregnant rats were treated with oral doses of 3, 10, and Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recom-mended human dose [MRHD] on a mg/m² basis) of aripipra-cole 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). There were no advance affects on embryofictal or nun survival. Delivered layed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered effspring 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 medi-ated through effects on female offspring) was seen at 30 mg/kg. 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.

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/m²) of aripiprazole during the period of orga-nogenesis. Decreased maternal food consumption and in-creased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fe-tal weight (30 and 100 mg/kg), increased incidence of skel-etal abortions were seen at 30 and 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/m² 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 de-creases in pup weight (persisting into adulthood) and sur-vival, were seen at medl-controlled studies in preg-nant 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 out-weighs the potential risk to the fetus. Labor and Delivery

weighs 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 an uning ractice was exercised in mix of rats ouring ractation. It is not known whether aripiprazole or its metabolities are ex-ceted in human milk. It is recommended that women re-ceiving aripiprazole should not breast-feed.

Pediatric Use Safety and effectiveness in pediatric and adolescent pa-tients have not been established.

Geriatric Use Genative Ose Of the 5592 patients treated with aripiprazole in premar-keting clinical trials, 659 (12%) were \geq 65 years old and 525 (9%) were \geq 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 pharma-collectance was decreased by 20% in elderly subjects (265 years), but there was no detectable effect of age in the pop-ulation pharmacokinetic analysis in schizophrenia patients. Studies of elderly patients with psychosis associated with Alzheimer's disease, have suggested that there may be a dif-ferent tolerability profile in this population compared to younger patients with concomitant Illness). The safety and efficacy of ABILIFY (aripiprazole) in the treatment of pa-tients 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. type. Placebo-controlled studies of aripiprazole in schizophrenia such patients with ABILIFY, vigilance should be exercised.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 5592 patients Aripiprazole has been evaluated for safety in 5592 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzhei-mer'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-induded (in overlapping categories) double-blind. compara-

ine contaisons and our atom or treatment with arripprazote included (in overlapping categories) double-blind, compar-tive and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and base and lower terms. 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 inves-

tigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dic-tionary terminology has been used initially to classify re-ported adverse events into a smaller number of standard-ized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing ad-verse events. verse events.

The stated frequencies of adverse events represent the pro-Ine stated requestes of adverse events represented approximation of individuals who experienced at least once, a treat-ment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the was considered treatment emergent in 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 The prescriber should be aware that the figure tables tables and tabulations cannot be used to predict the inci-dence of side effects in the course of usual medical practice where patient characteristics and other factors differ from 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, other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do pro-vide the prescribing physician with some basis for estimat-ing 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 arip-iprazole was administered in doses ranging from 2 to 30 mg/day.

30 mg/day Adverse Events Associated with Discontinuation of Treat

Adverse Events Associated with Discontinuation of Treat-ment in Short-Term, Placebo-Controlled Trials Overall, there was no difference in the incidence of discon-tinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar be-tween the configuracion and placebo-treated patients.

adverse events that led to discontinuation were similar be-tween the aripiprazole and placebo-treated patients. Adverse Events Occurring at an Incidence of 2% or More Among Aripiprazole-Treated Patients and Greater than Pla-cebo 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 $\geq 2 mg/day$) 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

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

¹ Events reported by at least 2% of patients treated with aripiprazole, except the following events, which had an in-cidence equal to or less than placebo: abdominal pain, ac-cidental injury, back pain, dental pain, dyspepsia, diarrhea, dry mouth, myalgia, agitation, psychosis, extrapyramidal syndrome, hypertonia, pharyngitis, upper respiratory tract infection. dysmenorrhea, vaginitis. 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 56%; 00 mg, 15 2%). Dose-Related Adverse Events 30 mg, was somnolen 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 In-Akatnisia Scale (for akatnisia), and the Assessments of In-voluntary Movement Scales (for dyskinesias) also did not show a difference between arripiprazole and placebo, with the exception of the Barnes Akathisia Scale (arripiprazole, 0.08; placebo, -0.05).

Laboratory Test Abnormalities A between group comparison for 4- to 6-week placebo-controlled trials revealed no medically important differcontrolled trials revealed no medically important differ-ences 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 aripipra-zole/placebo differences in the incidence of discontinuations for changes in serum chemistry hematology at uringlysis for changes in serum chemistry, hematology, or urinalysis. Weight Gain

In short-term trials, there was a slight difference in mean 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 \geq 7% of body weight (aripiprazole (8%) compared to placebo (3%)). The following table provides the weight change re-sults from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of \geq 7% of body weight rel-ative to baseline, categorized by BMI at baseline:

Table 2: Weig	ht Change Re Bas	sults Categoriz eline	ed by BMI at
Sector Sector	BMI <23	BMI 23-27	<u>BMI >27</u>
Mean change from baseline (kg)	2.6	1.4	-1.2
% with ≥7% increase BW	30%	19%	8%

ECG Changes

ECG Changes Between group comparisons for pooled, placebo-controlled trials revealed no significant differences between aripipra-zole 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. placebo patients.

Other Adverse Events Observed During the Premarketing

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 intro-duction to the ADVERSE REACTIONS section reported by patients treated with aripiprazole at multiple doses 22 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 AD-VERSE REACTIONS section, those considered in the WARNINGS or PRECAUTIONS, those event terms which 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 subwith an incidence of <0.05% and which did not have a sub-stantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is impor-tant to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

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 favor than 1/1000 natients.

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 – pel-vic pain, suicide attempt, face edema, malaise, photosensi-tivity, arm rigidity, jaw pain, chills, bloating, jaw tightness, enlarged abdomen, chest tightness; Rare – throat pain, back tightness, head heaviness. moniliasis. throat tightness, leg enlarged abdomen, chest tightness; Rare - throat pain, back tightness, head heaviness, moniliasis, throat pain, back cardiovascular System: Frequent - hypertension, tachy eardia, hypotension, bradycardia; Infrequent - palpitation, hemorrhage, myocardial infarction, prolonged QT interval, cardia carrest, atrial fibrillation, heart failure, AV block, myocardial ischemia, phlebitis, deep vein thrombosis, an-gina pectoris, extrasystoles; Rare - vasovagal reaction, car-diomegaly, atrial flutter, thrombophlebitis. Digestive System: Frequent - anorexia, nausea and vomit-ing; Infrequent - increased appetite, gastroenteritis, dys-

Digestive System: Frequent – anorexia, nausea ana vomit-ing: Infrequent – increased appetite, gastroenteritis, dys-phagia, flatulence, gastriis, tooth caries, gingivitis, hemor-hoids, gastroesophageal reflux, gastrointestinal hemorrhage, periodontal abscess, tongue edema, fecal in-continence, colitis, rectal hemorrhage, stomatitis, mouth ul-ex cholaeveitiis facel immedian oral moniliasis cholalithi. continence, contis, rectai nemorrnage, stomatuis, mouth ui-cer, cholecystitis, fecal impaction, oral moniliasis, cholelithi-asis, eructation, intestinal obstruction, peptic ulcer, Rare – esophagitis, gum hemorrhage, glossitis, hematemesis, me-lena, duodenal ulcer, cheilitis, hepatitis, hepatomegaly, pan-montific intestinal mechanism creatitis, intestinal perforation.

Continued on next page

Consult 2004 PDR[∞] supplements and future editions for revisions

Abilify-Cont.

Endocrine System: Infrequent - hypothyroidism; Rare goiter, hyperthyroidism. Hemic/Lymphatic System: Frequent -

ecchymosis, anemia; Infrequent - hypochromic anemia, leukopenia, leuko cytosis, lymphadenopathy, thrombocytopenia; Rare - eosin-ophilia, thrombocythemia, macrocytic anemia.

Metabolic and Nutritional Disorders: Frequent - weight loss, creatine phosphokinase increased; Infrequent - dehy-Joss, creatine phosphokinase increased; Infrequent – dehy-dration, edema, hypercholesteremia, hyperglycemia, hypokalemia, diabetes mellitus, SGPT increased, hyperlipe-mia, hypoglycemia, thirst, BUN increased, hyponatremia, SGOT increased, alkaline phosphatase increased, iron defi-ciency anemia, creatinine increased, bilirubinemia, lactic dehydrogenase increased, obesity; Rare – hyperkalemia, gout, hypernatremia, cyanosis, hyperuricemia, hypoglyce-mic reaction. mic reaction

Musculoskeletal System: Frequent - muscle cramp; Infre-quent - arthralgia, bone pain, myasthenia, arthritis, arthrosis, muscle weakness, spasm, bursitis; Rare - rhabdomyol-ysis, tendonitis, tenosynovitis, rheumatoid arthritis, myopathy.

Nervous System: Frequent - depression, nervousness, in-Nervous System: Prequent – depression, nervousness, in-creased salivation, hostility, suicidal thought, manic reac-tion, abnormal gait, confusion, cogwheel rigidity; Infrequent – dystonia, twitch, impaired concentration, paresthesia, vasodilation, hypesthesia, extremity tremor, impotence, bradykinesia, decreased libido, panic attack, apathy, dyski-nesia, hypersonnia, vertigo, dysarthria, tardive dyskinesia, ataxia, impaired memory, stupor, increased libido, amnesia, cerebrovascular accident, hyperactivity, depersonalization, hypothanica, restlues lear weedpenue, dempkrite, acurence hypokinesia, restless leg, mycolonus, dysphoria, neuropa-thy, increased reflexes, slowed thinking, hyperkinesia, hy-peresthesia, hypotonia, oculogyric crisis; *Rare* – delirium, euphoria, buccoglossal syndrome, akinesia, blumted affect, decreased consciousness, incoordination, cerebral ischemia, decreased reflexes, obsessive thought, intracranial hemmorhage.

Respiratory System: Frequent – dyspnea, pneumonia; In-frequent – asthma, epistaxis, hiccup, laryngitis; Rare – he-moptysis, aspiration pneumonia, increased sputum, dry nasal passages, pulmonary edma, 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 – maculo-papular rash, exfoliative dermatitis, urticaria.

Special Senses: Frequent - conjunctivitus, ear pain; Infre-quent - dry eye, eye pain, tinnitus, otitis media, cataract, altered taste, blepharitis; Rare - increased lacrimation, fre-quent blinking, otitis externa, amblyopia, deafness, diplo-pia, eye hemorrhage, photophobia. Urogenital System: Frequent - urinary incontinence; In-ference: Infrequent - urinary incontinence; In-

Urogenital System: Frequent – urinary incontinence; In-frequent – cystitis, urinary frequency, leukorrhea, urinary retention, hematuria, dysuria, amenorrhea, abnormal ejac-ulation, vaginal hemorrhage, vaginal moniliasis, kidney failure, uterus hemorrhage, menorrhagia, albuminuria, kid-ney calculus, nocturia, polyuria, urinary urgancy; 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 depen-dence. In physical dependence studies in monkeys, withdence in physical dependence studies in monkeys, with-drawal 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 mar-keted. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be ob-served 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 pa-tients taking the largest identified amount, 180 mg, the only tients taking the largest identified amount, 180 mg, the only symptoms reported were sommolence and vomiting in one of the two patients. In the patients who were evaluated in hos-pital 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 me) (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_e interval prolon-gation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxy-

Information will be superseded by supplements and subsequent edition

genation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

In the event of an overdose of ABILIFY Charcoal: (aripiprazole), an early charcoal administration may be use-ful in partially preventing the absorption of aripiprazole. In m particulty preventing the absorption of arpiprazole. Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of arpiprazole, decreased the mean AUC and C_{max} of arpiprazole by 50%. *Hemodialysis*: Although there is no information on the ef-fect of hemodialysis in treating an overdose with arpipra-

zole, hemodialysis is unlikely to be useful in overdose man-agement 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 dose in these tried lower and the rest of the target of 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 e, gender, race, or renal or hepatic impairment status CLINICAL PHARMACOLOGY: Special Populations).

Dosage adjustment for patients taking aripiprazole conco itantly with potential CYP3A4 inhibitors: When concost When concomitant administration of ketoconazole with aripiprazole oc-curs, 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 concom-itantly with potential CYP2D6 inhibitors: When concomi-tant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole oc-curs, aripiprazole dose should be reduced at least to onehalf of its normal dose. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

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All variables is a Wyeth Agerst Company. Dosage adjustment for patients taking potential CYP3A4 in-ducers: When a potential CYP3A4 inducer such as carba-mazepine 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 carba-mazepine 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

Switching from Other Antipsychotics There are no systematically collected data to specifically ad-dress switching patients with schizophrenia from other an-tipsychotics to ABILIFY or concerning concomitant admin-istration 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 articeyabite 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 $\rm mg/m^2$ 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 fol-

- ADLET 1⁻¹¹ (dipprazioe) radiets are available in the fol-lowing 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 Bister of 100 NDC 59148-007-35 The 10-mg ABILIFY tablets are pink, modified rectangu-lar tablets, debossed on one side with "A-008" and "10". Bottles of 30 NDC 59148-008-13
- Bitter of 100 NDC 59148-008-35 The 15-mg ABILIFY tablets are yellow, round tablets, de-bossed 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, de-bossed on one side with "A-010" and "20".

PHYSICIANS' DESK REFERENCE®

Bottles of 30	NDC 59148-010-13
Blister of 100	NDC 59148-010-35
The 30-mg ABILIFY table	ts are pink, round tablets, de-
bossed on one side with "A	-011" and "30".
Bottles of 30	NDC 59148-011-13
Blister of 100	NDC 59148-011-35
torage	
6° F) [see USP Controlled R	ions permitted to 15-30° C (59- com Temperature]. ca Pharmaceutical, Inc, Rock-
IL MD 00050 UGA	a Fharmaceutical, mc, noch

ville. 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

U.S. Patent Nos. 4,734,416 and 5,006,528 Bristol-Myers Squibb Company

Princeton, NJ 08543 U.S.A.	
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Pharmaceutical, Inc.	
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Tokyo, 101-8535 Japan	
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Shown in Product Identification Guide, page 310

AVALIDE®

Rx only

avă-līde] (irbesartan-hydrochlorothiazide) Tablets

USE IN PREGNANCY

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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 AVALDDE® (irbesartan-hydrochlorothiazide) Tablets is a combination of an angiotensin II receptor antagonis (AT₁ subtype), irbesartan, and a thiazide diuretic hydrochlorothiazide (HCTZ). Irbesartan is a non-peptide compound, chemically described as a 2-buty-3-[12'(1H-tetrazol-5-yl) [1, 1'-biphenyll-4] methyl]-1,3-diazaspiro [4,4] non-1-en-4-one. Its empiral formula is $C_{25}H_{23}N_6O$, and its structural formula is:

'N (CH₂)₂CH₂

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 chlo-

ride and practically insoluble in water. Hydrochlorothiazide is 6-chloro-3,4-dihydro- 2H-1,2,4-ben-zothiadiazine-7-sulfonamide 1,1-dioxide. Its empirical for mula is C7H8ClN3O4S2 and its structural formula is:



Hydrochlorothiazide is a white, or practically white, crystalline powder with a molecular weight of 291.7. Hydrochlorothiazide is slightly soluble in water and freely

Hydrochlorothiazide is slightly soluble in water and free soluble in sodium hydroxide solution. AVALIDE is available for oral administration in tablets on taining 150 mg or 300 mg of irbesartan combined with 12.5 mg of hydrochlorothiazide. Inactive ingredients in-clude: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, ferric oxide red, ferric oxide yellow, silicon dioxide, and magnesium stearate stearate.

CLINICAL PHARMACOLOGY

Mechanism Of Action Irbesartan

Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-conver-ing enzyme (ACE, kininase II). Angiotensin II is the princiang enzyme (ACE, kininase II). Angiotensin II is the print pal 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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STRATTERATM -[stră-těr-ă]

(atomoxetine HCI)

DESCRIPTION

DESCRIPTION STRATTERATM (atomoxetine HCl) is a selective norepi-nephrine reuptake inhibitor. Atomoxetine HCl is the $R(\cdot)$ isomer as determined by x-ray diffraction. The chemical designation is (\cdot) -N-methyl-3-phenyl-3-(c-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:

+ HCI

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

Each capsule contains atomoxetine HCl equivalent to 10. 18, 25, 40, or 60 mg of atomoxetine. The capsules also con-tain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and other in-active 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 Disor-

Information will be superseded by supplements and subsequent editions

der (ADHD) is unknown, but is thought to be related to selective inhibition of the pre-synaptic norepinephrine trans-porter, 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 glucuronida tion. Atomostine 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 pack plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine com-pared with people with normal activity [extensive metabo-lizers (EMs)]. Drugs that inhibit CYP2D6, such as fluxe-tine, 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 does 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.

similar. Absorption and Distribution—Atomoxetine is rapidly ab-sorbed after oral administration, with absolute bioavailabil-ity 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. Ad-

ministration of STRATTERA with a standard high-fat meal in adults did not affect the extent of oral absorption of In adults did not affect the extent of oral absorption of atomoxetine (AUC), but did decreases 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 dis-tributes primarily into total body water. Volume of distribution is similar across the patient weight range after normal-

tion is similar across the patient weight range after normal-izing 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 CVP2D6 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_{as,max} is about 5-fold greater than EMs. Laboratory tests are available to identify CVP2D6 PMs. Coadministration of STRATTERA identify CYP2D6 PMs. Caddministration of STRATTERA vith potent inhibitors of CYP2D6, such as fluoxetine, par-oxetine, or quinidine, results in a substantial increase in atomoxetine plasma exposure, and dosing adjustment may be necessary (see Drug-Drug Interactions). Atomoxetine did

to 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 concentra-tions (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine a control of the second substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentra-tions (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-desmethylato-moxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34 to 40 hours).

tetine 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 in-creased, 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 insuf-ficiency. Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency (see DOSAGE AND ADMINISTRATION).

Renal insufficiency—EM subjects with end stage renal dis-ease 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 doe. STRATTERA can therefore be administered to ADHD pa STAAT ISRA can therefore be administered to ADHD pe-tients with end stage renal disease or lesser degrees of real insufficiency using the normal dosing regimen. <u>Geriatric</u>—The pharmacokinetics of atomoxetine have not been evaluated in the geriatric population. <u>Pediatric</u>—The pharmacokinetics of atomoxetine in child-

ren and adolescents are similar to those in adults. The phar ren and adolescents are similar to those in adults. The phar-macokinetics of atomoxetine have not been evaluated in children under 6 years of age. <u>Gender-Gender did not influence atomoxetine disposition.</u> <u>Ethnic origin</u>—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 concen-trations to exposures similar to those observed in PMs. Doage adjustment of STRATTERA in EMs may be necessary when coadministered with CYP2D6 inhibitors, e.g., parox etine, fluoxetine, and quinidine (see Drug Interactions un-der PRECAUTIONS). In vitro studies suggest that cost ministration 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 g

Albuterol—Albuterol (600 mcg iv over 2 hours) induced in-

creases 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 albutered and atomoxetine (see Drug-Drug Interactions under PRECAUTIONS).

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

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

Methylphenidate—Coadministration of methylphenidate with STRATTERA did not increase cardiovascular effects

which STRATTERA the not increase carboxisecular enter beyond those seen with methylphenidate alone. Midazolam—Coadministration of STRATTERA (60 mg BU for 12 days) with midazolam, a model compound for CYP3A4 metabolized drugs, (single does of 5 mg), result in 15% increase in AUC of midazolam. No does adjustment in concentration of the does o

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, actyl salicylic acid, phenytoin, or diazepam to human albur Similarly, these compounds did not affect the binding of atomoxetine to human albumin.

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

CLINICAL STUDIES

The effectiveness of STRATTERA in the treatment of ADED was established in 6 randomized, double-blind, placeb-controlled studies in children, adolescents, and adults wh met Diagnostic and Statistical Manual 4th edition (DSM/I) criteria for ADHD (see INDICATIONS AND USAGE). Children and Adolescents The effectiveness of STRATTERA in the treatment of ADHD

The energy of STRATERA in the treatment of ADW was established in 4 randomized, double-blind, placeke controlled studies of pediatric patients (ages 6 to 18). Ap-proximately one-third of the patients met DSM-IV criteri for inattentive subtype and two-thirds met criteria for bar inattentive and hyperactive/impulsive subtypes (see IND-CATIONS 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 interbrust Hink' and placebord cate patients using an inter-to-treat analysis of the primary outcome measure, the is-vestigator administered and scored ADHD Rating Scale!V Parent Version (ADHDRS) total score including hyperactive/impulsive and inattentive subscales. Each ite on the ADHDRS maps directly to one symptom criterion fit ADHD in the DSM-IV.

ADID in the DSM-V. In Study 1, an 8-week randomized, double-blind, place controlled, dose-response, acute treatment study of childre and adolescents aged 8 to 18 (N=297), patients received e ther a fixed dose of STRATTERA (0.5, 1.2, or 1.6 mg/kg/dg) 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 At the 2 higher doses, improvements in ADHD symptom were statistically significantly superior in STRATTERA-treated patients compared with placebo-treated patients measured on the ADHDRS scale. The 1.8-mg/kg/day STRATTERA dose did not provide any additional beefs 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 adoles cents aged 6 to 16 (N=171), patients received either STRATTERA or placebo. STRATTERA was administered a

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a single dose in the early morning and titrated on a weight-adjusted basis according to clinical response, up to a maxiadjusted basis according to clinical response, up to a maxi-mum 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 ef-facting when administered one daily in the merging

ADELING Scale. This study shows that STRATTERA 18 er-schive 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 methylpheni-date were compared with placebo. STRATTERA was admin-date were compared with placebo. STRATTERA was admin-tered as a divided done in the apply merging and late istered 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 recom-mended STRATTERA dose was 2.0 mg/kg/day. The mean fi-nal dose of STRATTERA for both studies was approximately 16 mg/kg/day. In both studies was approximately 16 mg/kg/day. In both studies, ADHD symptoms statisti-ally significantly improved more on STRATTERA than on alacebo, as measured on the ADHDRS scale.

pacero, as measured on the ADADA state. Examination of population subsets based on gender and age (<12 and 12 to 17) did not reveal any differential responness on the basis of these subgroupings. There was not afficient exposure of ethnic groups other than Caucasian to allow exploration of differences in these subgroups. dult

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

Mater, who met DSM-1V 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 pri-mary effectiveness measure was the 18-item Total ADHD Symptom score (the sum of the inattentive and hyperactiv-dimmulsivity subscales from the (CAARS) aujusted by a hympulsivity subscales from the CAARS) evaluated by a sumparison of mean change from baseline to endpoint using m intent-to-treat analysis.

in interview analysis. h 2 identical, 10-week, randomized, double-blind, placebo-ostrolled acute treatment studies (Study 5, N=280; Study 5, N=256), patients received either STRATTERA or placebo. STRATTERA was administered as a divided dose in the and and and and a second The mean final dose of STRATTERA for both studies was are near that upset of STAATTERA for both studies was approximately 95 mg/day. In both studies, ADHD symptoms were statistically significantly improved on STRATTERA, is measured on the ADHD Symptom score from the CAARS

Examination of population subsets based on gender and age (<42 and ≥42) did not reveal any differential responsive</p> ess on the basis of these subgroupings. There was not suffcient exposure of ethnic groups other than Caucasian to ow exploration of differences in these subgroups.

NDICATIONS AND USAGE

STRATTERA is indicated for the treatment of Attention

Deficit/Hyperactivity Disorder (ADHD). The effectiveness of STRATTERA in the treatment of ADHD as established in 2 placebo-controlled trials in children, 2 lacebo-controlled trials in children and adolescents, and 2 lacebo-controlled trials in adults who met DSM-IV criteria MADHD (see CLINICAL STUDIES).

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 mptoms must be persistent, must be more severe than is pically observed in individuals at a comparable level of deelopment, must cause clinically significant impairment, g, in social, academic, or occupational functioning, and eg. 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 fr by another mental disorder. For the Inattentive Type, at kast 6 of the following symptoms must have persisted for at last 6 months: lack of attention to details/careless mis-tikes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks re-quiring sustained mental effort, loses things; easily dis-meted forzeful. For the Hymerective Impulsive Type, at ted, forgetful. For the Hyperactive-Impulsive Type, at and of the following symptoms must have persisted for at at 6 of the following symptoms must have persisted for at at 6 months: fidgeting/squirming, leaving seat, inappro-iate running/climbing, difficulty with quiet activities, "on and interruption of the second Special Diagnostic Considerations

he specific etiology of ADHD is unknown, and there is no ingle diagnostic test. Adequate diagnosis requires the use attonly of medical but also of special psychological, educaas only of medical but also of special psychological, educa-binal, and social resources. Learning may or may not be mained. The diagnosis must be based upon a complete his-tory and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Meet for Comprehensive Treatment Program STRATTERA is indicated as an integral part of a total treat-ment program for ADHD that may include other measures (sychological, educational, social) for patients with this indome. Drug treatment may not be indicated for all pa-lents with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to anyionmental factors and/or other primary psychiatric diserders, including psychosis. Appropriate educational place-ment 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 more than 9 weeks in child and adolescent patients and 10 weeks in adult patients, has not been systematically evalu-ated 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 in-dividual 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, rious, sometimes fatal, reactions (including hyperthermia, n-gidity, 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 angio neurotic 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 atomsteine does, 1.3%, 7.1%, 19.3%, and 29.1% of patients lost at least 3.5% of their body weight in the pla-cebo, 0.5, 1.2, and 1.8 mg/kg/day STRATTERA does groups, respectively. During actual te magnegical STRATTERA dose groups, respectively. During actual 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 rowth were compared to correct events. 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 vas lower for poor metabolizer (PM) patients compared with extensive metabolizer (EM) patients (+0.7 kg com-pared with +3.0 kg), while mean growth for PM patients pared 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 treat-ment 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, follow-ing STRATTERA dose increases, and periodically while on therapy.

In pediatric placebo-controlled trials, STRATTERA-treated In pediatric piaceno-controued trials, SIRAI LDRA-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% (1004) of elecobe outpiets. Mo 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 Increases of about 1.5 mm Hg m systolic and diastolic blood pressures compared with placeb. At the final study visit be-fore drug discontinuation, 6.8% (22/324) of STRATTERA-treated pediatric subjects had high systolic blood pressure measurements compared with 3.0% (6/197) of placebs sub-jects. High systolic blood pressures were measured on 2 or more conscisues in 8.2% (26/204) of STPATTERAmore 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 sub-jects. (High systolic and diastolic blood pressure measure-ments were defined as those exceeding the 95th percentile, stratified by age, gender, and height percentile - National High Blood Pressure Education Working Group on Hyper-tension Control in Children and Adolescents.) In adult placebo-controlled trials, STRATTERA-treated

tension Control in Children and Anotescents.) 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. cebo subjects.

STRATTERA-treated adult subjects experienced mean in-STRATTERA-treated adult subjects experienced mean in-creases in systolic (about 3 mm Hg) and diastolic (about 1 mm Hg) blood pressures compared with placeb. At the final study visit before drug discontinuation, 1.9% (5/258) of STRATTERA-treated adult subjects had systolic blood pres-sure measurements =150 mm Hg compared with 1.2% (3/ 256) of placebo subjects. At the final study visit before drug discontinuation, 0.8% (2257) of STRATTERA-treated adult subjects had diastolic blood pressure measurements. subjects had diastolic blood pressure measurements $\geq 100 \text{ mm Hg compared with } 0.4\% (1/257) \text{ of placebo sub-$ jects. No adult subject had a high systolic or diastolic blood

pressure detected on more than one occasion. Orthostatic hypotension has been reported in subjects tak-ing STRATTERA. In short-term child- and adolescent-controlled trials, 1.8% (6/340) of STRATTERA-treated subjects experienced symptoms of postural hypotension com-pared with 0.5% (1/207) of placebo-treated subjects. STRATTERA should be used with caution in any condition

STRAITERA 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 the patient of the patient of the packet of the pa 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-con nter medie

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 pos-sible, 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. aboratory Tests

Laboratory Tests Routine laboratory tests are not required. <u>CYP2D6</u> metabolism-Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concen-tration to a given dose of STRATTERA compared with ex-tensive metabolizers (EMs). Approximately 7% of a Cauca-sian 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 REAC-TIONS).

Drug-Drug Interactions:

Albuterol-STRATTERA should be administered with caution to patients being treated with systemically-adminis-tered (oral or intravenous) albuterol (or other beta ago-nists) because the action of albuterol on the cardiovascular system can be potentiated.

System can be potentiated. <u>CYP2D6</u> inhibitors—Atomoxetine is primarily metabolized by the <u>CYP2D6</u> pathway to 4-hydroxyatomoxetine. In EMs, selective inhibitors of <u>CYP2D6</u> 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 in-hibitors, e.g., paroxetine, fluoxetine, and quinidine (see DOSAGE AND ADMINISTRATION). In EM individuals treated with conserving and the individuals bosade and administration). In the individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and $C_{as,max}$ 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

Consult 2004 PDR[®] supplements and future editions for revisions

Strattera-Cont.

Monoamine oxidase inhibitors— See CONTRAINDICA-TIONS.

nts-Because of possible effects on blood pres-Pressor agents—Because of possible effects on blood pres-sure, 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 455 mg/kg/day, respec-tively. The highest dose used in rats is approximately 8 and 5 times the maximum human dose in children and adults, respectively, on a mg/m² 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 metaboliz-ers) those in humans receiving the maximum human dose. times (extensive metabolizers) or 0.2 times (poor metaboliz-ers) 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, re-spectively, on a mg/m² basis. Mutagenesis—Atomoxetine HCl was negative in a battery of genotoxicity studies that included a reverse point muta-tion assav (Ames Test). an in vitro mouse lymphoma assav.

of genotoxicity studies that included a reverse point muta-tion 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 hepato-cytes, 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 en-doreduplication (numerical aberration). The metabolite N-desmethylatomoxetine HCI was negative in the Ames Test, mouse lymphoma assay, and unscheduled

in the Ames Test, mouse lymphoma assay, and unscheduled DNA synthesis test.

DNA synthesis test. <u>Impairment of fertility</u>—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/m² 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/m² basis; plasma levels (AUC) of atomoxetine at this dose in rabbits are esti-mated to be 3.3 times (extensive metabolizers) or 0.4 times mated to be 3.3 times (extensive metabolizers) or 0.4 times (poor metabolizers) those in humans receiving the maxium human dose

num 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/m² basis) in the diet from 2 weeks (females) or 10 weeks (males) prior to mating through the periods of or-ganogenesis 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 de-crease 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/m² basis) but not at 20 mg/kg/day.

at 20 mg/kg/day. No adverse fetal effects were seen when pregnant rats were

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/m² basis) by gavage throughout the period of organogenesis. No adequate and well-controlled studies have been con-ducted in pregnant women. STRATTERA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Labor and Deliverv

Labor and Delivery Parturition in rats was not affected by atomoxetine. The ef-fect of STRATTERA on labor and delivery in humans is unknown

Nursing Mothers

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 efficacy of STRATTERA beyond 9 weeks and safety of STRATTERA beyond 1 year of treatment have not been systematically evaluated.

tematically 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/m² basis) of atomoxetine given by gavage from the early postnatal period (Day 10 of age) 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 inci-sor eruption was seen at 50 mg/kg. A slight increase in mo-tor activity was seen on Day 15 (males at 10 and 50 ms/kg tor activity was seen on Day 15 (males at 10 and 50 mg/kg

Information will be superseded by supplements and subsequ ent editions

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 learn-ing and memory tests. The significance of these findings to mans 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 adoles-cent patients with ADHD and 270 adults with ADHD in

cent patients with ADHD and 2707 enhanced to adolese cent patients with ADHD and 2707 adults with ADHD in clinical studies. During the ADHD clinical trials, 169 pa-tients 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 esti-mating the relative contribution of drug and non-drug fac-tors to the adverse event incidence in the population studied. studied.

Child and Adolescent Clinical Trials

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 dis-continued for adverse events. For all studies, (including open-label and long-term studies), 5% of extensive metabo-lizer (EM) patients and 7% of poor metabolizer (PM) pa-tients discontinued because of an adverse event. Among STRATTERA-treated patients, aggression (0.5%, N=2); irri-tability (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.

(0.5%, N=2) were the reasons to takentinearies replaced by more than 1 patient. <u>Commonly observed adverse events in acute child and ado-lescent, placebo-controlled trials</u>—Commonly observed ad-verse events associated with the use of STRATTERA (inci-verse) verse events associated with the use of STRATTERA (inci-dence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (STRATTERA in-cidence 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 ad-verse events in patients treated with STRATTERA (inci-dence of 5% or greater and at least twice the incidence in dence 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, dizzi-ness, 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	
ganal. Al ar taonaí alta San Signeraithe altar	STRATTERA (N=340)	Placebo (N=207)
Gastrointestinal Disorders	- Heren alters	n -mysa din
Abdominal pain upper	20	16
Constipation	3	general line
Dyspepsia	4	2

Vomiting	. 11	9
nfections	An Bern in St. Information State	A SAR
Ear infection	3	1
Influenza	3	1
Investigations	V- water it	a Dambi
Weight decreased	2	· · · · · · · 0
Metabolism and Nutritional Disorders	la de sua géner para logala	t in di b di e ope
Appetite decreased	14	6
Nervous System Disorders	t distant in the second	COMP B
Dizziness (exc vertigo)	6	.3
Headache	27	25
Somnolence	7	5
Psychiatric Disorders		- shit
Crying	2	1
Irritability	8	5
Mood swings	2	0
Respiratory, Thoracic, and Mediastinal Disorders	Constraints April 10 Constraints April 10	n in angele States angele Na sangele
Cough	. 11	7
Rhinorrhea		3
Skin and Subcutaneous Tissue Disorders	n na na mantana na anina (na da na mana anina	
Dermatitis	4	11 11 11 11 11 11 11 11 11 11 11 11 11

¹Events 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 treat-ment: anorexia, blood pressure increased, early morning awakening, flushing, mydriasis, sinus tachycardia, tar-fulness. The following events were reported by at least 35 of patients treated with atomoxetine, and equal to riss sthan placebo: arthrafaja, gastroenteritis viral, insonna, sore throat, nasal congestion, nasopharyngitis, prurius sinus congestion, upper respiratory tract infection.

[See table 2 below]

[See table 2 below] The following adverse events occurred in at least 2% of PM patients and were either twice as frequent or statistical significantly more frequent in PM patients compared with EM patients: decreased appetite (33% 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); tremer (6# PMs, 1% of EMs); early morning awakening (3% of PMs, 1% of EMs); pruritus (2% of PMs, 1% of EMs); mydriasis (2% d PMs, 1% of EMs). Addut Clinical Trials

Adult Clinical Trials

Adult Clinical Trials Reasons for discontinuation of treatment due to adverse events in acute adult placebo-controlled trials—In the acut adult placebo-controlled trials, 8.5% (23/270) atomoteize 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

dverse Event Percentage of Patients Reporting Events from BID Trials		Percentage of Patients Reportin Events from QD Trials		
[1] A. J. Ling, "The second s Second second sec	STRATTERA (N=340)	Placebo (N=207)	STRATTERA (N=85)	Placebo (N=85)
Gastrointestinal Disorders	- Carlor and the state	i an white arthur which	a ana ba guna. A Setual dinte	
Abdominal pain upper	20	16	. 16	9
Constipation	- 15 Fa 3	1	interiore O Charlenge -	0
Diarrhea	3	6	4 d	50-500 1
Dry mouth	1	2 2		1 i 1
Dyspepsia	-		8	inda se 0
Nausea	7	8 monaci	12	2
Vomiting	11	9	15	1
General Disorders	10. que 1. 10	an a	 Mary + 1/2 (2019) Mary + 1/2 (2019) 	
	4	5	9	1
Fatigue	e contraction of	1 10 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	The second second second	中心学校的研究
Psychiatric Disorders	Semigravity 1 12	The Island Sec.	a sendana sala a	2
Mood swings	2	0	to here 5	100.00

PRODUCT INFORMATION

adverse events. Among STRATTERA-treated patients, in-sommia (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 placebo-treated patients (STAATIEAA incluence 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, de-creased libido, ejaculatory problems, impotence, urinary hesitation and/or urinary retention and/or difficulty in mic-turition, 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	S and north	a chung	
Palpitations	4	1	
Gastrointestinal Disorders	(Alexandra)	(10 ¹) ⁽¹ = 1 1	
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	$= 1_{i_1 i_2 i_3}^{i_1 i_3 i_4} 1_{i_1 i_2 i_3}^{i_3 i_4 i_3 i_4}$	
Infections	1999) - 1992(1) (j.	0.0002000	
Sinusitis	6	4	
Investigations	a set contents	1. 1124	
Weight decreased	2	1	
Metabolism and Nutritional Disorders	$\frac{1}{2} = \frac{1}{2} $	a internation di Adapit anternation	
Appetite decreased	10	3	
Musculoskeletal, Connective Tissue, and Bone Disorders	Registration of the second	61 - (139 1741 - 1 1749 - 1	
Myalgia	3	2	
Nervous System Disorders	1.41	201	
Dizziness	6	2	
Headache	17	17	
Insomnia and/or middle insomnia	16	8	
Paraesthesia	4	2	
Sinus headache	3	1	
Psychiatric Disorders	12211210.008	1.1.1.2	
Abnormal dreams	4	3	
Libido decreased	6	2	
Sleep disorder	4	2	
Renal and Urinary Disorders	A the second second	12.64	
Urinary hesitation and/or urinary retention and/or difficulty in micturition	international and an entropy and a second second 8	0	
Reproductive System and Breast Disorders		1 - 110 2 V	
Dysmenorrhea ³	7	3	

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:	11° - 10,223	Antal Contactor	-19 "Ca" 80 040	1. 11 - 11 a	1000
Bottles of 30	0002-3227-30	0002-3238-30	0002-3228-30	0002-3229-30	0002-3239-30

"Atomoxetine base equivalent.		
Ejaculation failure ² and/or ejaculation disorder ²	ant to a superior accessor to the second to a 5 Second	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	and an ann an Anna an Anna An An Anna Anna	and and a second se Second second second Second second
Dermatitis	2	1
Sweating increased	4	1
Vascular Disorders		
Hot flushes	3	1

¹Events 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 note atomotechie treated patients in patients other patients and are possibly related to atomoxetine treat-ment: 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, naso-pharyngitis, sore throat, upper respiratory tract infection, vomiting. ²Based 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 sex-ual 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 ac-tual 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.

	4	

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

There are no adequate and well-controlled studies examin-There are no acquate and well-controller sources examine ing 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.

STRATIERA 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.

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 inappro-priate self-administration associated with STRATTERA. There was no evidence of symptom rebound or adverse events suggesting a drug-discontinuation or withdrawal syndrome

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 rec-ommended daily dose in humans are unknown.

ommended daily dose in numers 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 sup-portive care. Gastric emptying and repeated activated charcoal (with/without cathartics) may prevent systemic absorption

DOSAGE AND ADMINISTRATION Initial Treatment

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 min-imum 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).

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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 admin-istered 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 of a maximum of 100 mg in patients who have not achieved an optimal response. There are no data that support increased effectiveness at hicher doses (see CLINIsupport increased effectiveness at higher doses (see CLINI-CAL 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 in-There is no evolution available from control of the second dicate 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 ex-tended periods. Nevertheless, the physician who elects to use STRATTERA for extended periods should periodically valuate 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

The statety 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-Puph Class B), initial and target doses should be reduced to 50% of the normal dose (for pa-tients 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 inhibi-tor-In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluxetine, 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

In children and addressents over 10 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., parox-etine, fluoxetine, and quinidine, STRATTERA should be ini-tiated at 40 mg/day af 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

* 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 quiry to Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana 46285, (800) 545-5979.

Consult 2004 PDR® supplements and future editions for revisions

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™

STRATTERA'" (atomoxetine HCI) 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?

What is STRATTERA/ STRATTERA is a non-stimulant medicine used to treat At-tention.Deficit/Hyperactivity Disorder (ADHD). STRAT-TERA contains atomoxetine hydrochloride, a selective nor-epinephrine reuptake inhibitor. Your doctor has prescribed this medicine as part of an overall treatment plan to control your symptoms of ADHD.

What is ADHD?

What is ADHD? ADHD has 3 main types of symptoms: inattention, hyperac-tivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listen-ing, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsive-ness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some pa-tions have near symptomes of hyperactivity and impulsive-tions have near symptomes of hyperactivity and impulsive-hyperactivity. tients have more symptoms of hyperactivity and impulsive-ness 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, day-dreaming, daytime drowsiness, slow processing of informa-tion, difficulty learning new things, irritability, lack of motivation, sensitivity to criticism, forgetfulness, low self-esteem, and excessive effort to maintain some organization. esteem, and excessive error to maintain some organization. The symptoms shown by adults who primarily have atten-tion 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. Sumptome much be version for at heart 6

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:
- u took a medicine known as a monoamine oxidase inyou took a medicine known as a monoamine oxidase in-hibitor (MAOI) in the last 2 weeks. An MAOI is a med-icine sometimes used for depression and other mental
- terne sometimes used for depression and other methods 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 ingredi-

ents. 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 heart-beat. STRATTERA can increase heart rate (pulse).
 have low blood pressure. STRATTERA can cause dizzi-
- ness 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 medi-cines, dietary supplements, and herbal remedies. Your doctor will decide if you can take STRATTERA with your other medicines.

medicines. Certain medicines may change the way your body reacts to STRATTERA. These include medicines used to treat depres-sion [like Paxil[®] (paroxetine) and Prozae[®] (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 meinteneeus calbuterd (are drugs with similar actions) but

or intravenus 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.

- Ing abouterol. 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 pefoin
- Taking STRATTERA at the same time each day may help ou 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 pre-scribed dose of STRATTERA.

Other important safety information about STRATTERA Use caution when driving a car or operating heavy machin-ery until you know how STRATTERA affects you. Talk to your doctor if you are

· pregnant or planning to become pregnant

Information will be superseded by supplements and subsequent editions

· 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 teen-agers 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 STRAT-TERA 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

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. Active ingredients: atomoxedne. 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® HCI [văn 'kō-sĭn āch 'sē-ĕl] capsules, USP)

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

DESCRIPTION

DESCRIPTION Pulvules® Vancocin® HCl (Vancomycin Hydrochloride Capsules, USP) contain chromatographically purified vancomycin hydrochloride, a tricyclic glycopeptide antibi-otic derived from Amycolatopsis orientalis (formerly Nocar-dia orientalis), which has the chemical formula formula formula formula CegeH₇₅CLN₉O₂₄*HCl. The molecular weight of vancomycin hydrochloride is 1,485.73; 500 mg of the base is equivalent the O Cemican Comparison of the base is equivalent to 0.34 mmol.

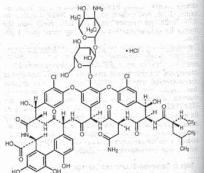
to 0.94 mmol. The Pulvules contain vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The Pulvules also contain F D & C Blue No. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredies

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 concentraPHYSICIANS' DESK REFERENCE®



tions 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 meaease, blood concentrations of vancomycin were barely mesurable (0.66 µg/mL) in 2 of 5 subjects who received 2 g df Vancoin HCl for Oral Solution daily for 16 days. No mesurable blood concentrations were attained in the other 3 patients. With doses of 2 g daily, very high concentrations d'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 collists. Orally administered vancomverin dose not new the serum of patients with normal renal function who have pseudomembranous collists. Orally administered vancomverin dose not new the serum of patients of the serum of patients with normal renal function who have pseudomembranous collists. nous colitis. Orally administered vancomycin does not use ally enter the systemic circulation even when inflammatory any enter the systemic circulation even when inflammator lesions are present. After multiple-dose oral administration of vancomycin, measurable serum concentrations may infr-quently occur in patients with active *C. difficile*-induced pseudomembranous colitis, and, in the presence of renaliz-pairment, the possibility of accumulation exists.

Microbiology-The bactericidal action of vancomycin result primarily from inhibition of cell-wall biosynthesis. In add tion, vancomycin alters bacterial-cell-membrane permeabi-ity 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 set tion. 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 infectors as described in the INDICATIONS AND USAGE sector.

Aerobic gram-positive microorganisms Staphylococcus aureus (including methicillin-resistant strains) associated with enterocolitis

Anaerobic gram-positive microorganisms Clostridium difficile antibiotic-associated pseudomembra-

nous colitis

INDICATIONS AND USAGE

Vancocin HCl Pulvules may be administered orally fir treatment of enterocolitis caused by Staphylococcus aureat (including methicillin-resistant strains) and antibiotiassociated pseudomembranous colitis caused by C. dificile Parenteral administration of Vancocin HCl is not effective for the above indications; therefore, Vancocin HCl must a 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 bypersensitivity to this antibiotic.

PRECAUTIONS

R

General—Clinically significant serum concentrations has been reported in some patients who have taken multip-oral doses of vancomycin for active C. difficile-induced pse-domembranous colitis; therefore, monitoring of serum an centrations may be appropriate in some instances, eg in pa-tients with renal insufficiency and/or colitis.

Some patients with inflammatory disorders of the intestinal Some patients with inflammatory disorders of the intestinal nucosa may have significant systemic absorption of vancomycin and, therefore, may be at risk for the develop ment of adverse reactions associated with the parenter administration of vancomycin. (See package insert accom-panying the intravenous preparation.) The risk is greater frenal impairment is present. It should be noted that the is tal systemic and renal clearances of vancomycin, are in duced in the elderly. duced in the elderly.

duced in the elderly. Ototoxicity has occurred in patients receiving Vancoin Hi It may be transient or permanent. It has been report mostly in patients who have been given excessive intra-ne and the second second second second second second are receiving concomitant therapy with another ottan agent, such as an aminoglycoside. Serial tests of azimy function may be helpful in order to minimize the rak of ototoxicity ototoxicity. When patients with underlying renal dysfunction or those

receiving concomitant therapy with an aminoglycoside ar-being treated, serial monitoring of renal function should be

performed. Use of vancomycin may result in the overgrowth of no ceptible organisms. If superinfection occurs during therap,

appropriate measures should be taken. Carcinogenesis, Mutagenesis, Impairment of Fertilitylong-term carcinogenesis studies in animals have been con ducted.

(vancomycin hydrochloride

Ultram-Cont.

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

Labor and Delivery

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 depen-dence and post-partum withdrawal symptoms in the new-born (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 mater-nal veins was 0.83 for 40 women given tramadol during labor labor

The effect of ULTRAM, if any, on the later growth, develop-ment, and functional maturation of the child is unknown. Nursing Mothers

ULTRAM is not recommended for obstetrical preoperative ULTRAM is not recommended for obsectrical preoperative medication or for post-delivery analgesia in nursing moth-ers 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 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 CLIN-ICAL PHARMACOLOGY and DOSAGE AND ADMINIS-TRATION) TRATION).

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 In studies including genatic patients, treatment-initian 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 treatmentlimiting 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 dou ULTRAM was administered to 550 patients during the dou-ble-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 fre-quently reported events were in the central nervous system and gastrointestinal system. Although the reactions listed in the table are fielt to be probably related to ULTRAM ad-ministration, the removated rates also include some events ministration, the reported rates also include some events that may have been due to underlying disease or concomithat may have been due to underlying disease or concomi-tant medication. The overall incidence rates of adverse ex-periences in these trials were similar for ULTRAM and the active control groups, TYLENOL® with Codeine #3 (ace-taminophen 300 mg with codeine phosphate 30 mg, and as-pirin 325 mg with codeine phosphate 30 mg, however, the rates of withdrawals due to adverse events appeared to be history in the UUTPAM comment. 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%

"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.

Information will be superseded by supplements and subsequent editions

Central Nervous System: Anxiety, Confusion, Coordina-tion disturbance, Euphoria, Miosis, Nervousness, Sleep disorder.

Abdominal pain, Anorexia, Flatulence. Gastrointestinal: 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 inci-dence 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, Seroto-nin syndrome (mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma).

Cardiovascular: Orthostatic hypotension, Syncope, Tachycardia.

Central Nervous System: Abnormal gait, Amnesia, Cogni-tive dysfunction, Depression, Difficulty in concentration, Hallucinations, Paresthesia, Seizure (see WARNINGS), Tremor.

Respiratory: Dyspnea. Skin: Stevens-Johnson syndrome/Toxic epidermal necroly-sis, Urticaria, Vesicles.

Special Senses: Dysgeusia.

Urogenital: Dysuria, Menstrual disorder. Other adverse experiences, causal relationship unknown: A variety of other adverse events were reported infrequently variety of other adverse events were reported infrequently in patients taking ULTRAM during clinical trials and/or re-ported in post-marketing experience. A causal relationship between ULTRAM and these events has not been deter-mined. However, the most significant events are listed be-low as alerting information to the physician. Cardiovascular: Abnormal ECG, Hypertension, Hypo-tension, Myocardial ischemia, Palpitations, Pulmonary edvere. Pulmocaru ambdium.

edema, Pulmonary embolism. Central Nervous System: Migraine, Speech disorders. Gastrointestinal: Gastrointestinal bleeding, Hepatitis,

Gastrointestinai. Gastrointestinai bicodag, replanas Stomatiis, Liver failure. Laboratory Abnormalities: Creatinine increase, Elevated liver enzymes, Hemoglobin decrease, Proteinuria. Sensory: Cataracts, Deafness, Tinnitus.

DRUG ABUSE AND DEPENDENCE

DRUG ABUSE AND DEPENDENCE ULTRAM may induce psychic and physical dependence of the morphine-type (u-opioid). (See WARNINGS.) Depen-dence and abuse, including drug-seeking behavior and tak-ing 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: anxiet, weating, insomia, rizors, pain, nausea, tremors, 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 reduc-tion of the medication combined with symptomatic support.

OVERDOSAGE

Serious potential consequences of overdosage are respira-Serious potential consequences of overdosage are respira-tory depression, lethargy, coma, seizure, cardiac arrest and death. (See WARNINGS) Fatalities have been reported in post marketing in association with both intentional and un-intentional overdose with ULTRAM. In treating an over-dose, primary attention should be given to maintaining ad-equate 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 pelvone administration. In animalis caused by overdosage with ULIKAAA, the risk of seizures is also increased with haloxone administration. In animals convulsions following the administration of toxic doses of tramadol could be suppressed with barbiturates or benzodi-azepines but were increased with haloxone. Naloxone ad-ministration did not change the lethality of an overdose in ministration diduction is a constant to be halphilp in an overmine. Hemodialysis is not expected to be helpful in an over-dose 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 toler-ability of ULTRAM can be improved by initiating therapy with the following titration regimen: ULTRAM should be 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 admin-istered 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

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/ it is recommended that the dosing interval of 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 or correct 12 hours. min.

The recommended dose that preserves a second years on should be callous, usually scaling as the be-end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of con-comitant disease or other drug therapy. For elderly pa-tients over 75 years old, total dose should not exceed 300 mg/day.

HOW SUPPLIED

HOW SUPPLIED ULTRAM (tramadol hydrochloride tablets) Tablets -50 mg (white, scored, film-coated capsule-shaped tablet) debased "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 bijster packs -

NDC 0045-0659-10 (10 cards of 10 tablets each). Dispense in a tight container. Store at 25°C (77°F); exar-sions 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

7517003 MP 2001 Revised August 2001 751 Shown in Product Identification Guide, page 330 © OMP 2001

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ABILIFY [ă-bil-ifi] (aripiprazole) Tablets B only

DESCRIPTION

DESCRIPTION ABILIFY^{IM} (aripiprazole) is a psychotropic drug that is available as tablets for oral administration. Aripiprazole's 7-[4,[4,2,3-dichloropheny])-1-piperaziny]]butoxy]-3,4diby- $drocarbostyril. The empirical formula is <math>C_{28}H_27(C_1N_0)$ 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 lac tose monohydrate, cornstarch, microcrystalline cellulose hydroxypropyl cellulose, and magnesium stearate. Col-rants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY Pharmacodynamics Aripiprazole exhibits high affinity for dopamine D_2 and D_3 serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K, values of 034, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity for b-pamine D_4 , serotonin 5-HT_{2C} and 5-HT₇, alpha₁-adrenergie and histamine H, receptors (K, values of 44, 15, 39, 67, ad 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K₁=98 nM). Aripiprazole has no appresiable affinity for cholinergic muscarinic receptors (ICs >1000 nM). Aripiprazole functions as a partial agoinst 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. Bor-ever, it has been proposed that the efficacy of aripiprazels mediated through a combination of partial agoinst ativity

ever, it has been proposed that the efficacy of aripipraale is mediated through a combination of partial agonist activity at D₂ and 5-HT₁, receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D₃ 5-HT_{1Ab}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole, e.g., the orthostatic hypotension de-served with aripiprazole may be explained by its antagonist activity at adrenergic alpha₁ receptors. Pharmacokinetics

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

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PHYSICIANS' DESK REFERENCE®

RODUCT INFORMATION

abilite, dehydro-aripiprazole, which has been shown to bre affinities for D_2 receptors similar to the parent drug airpresents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 purs for aripiprazole and dehydro-aripiprazole, respec-nely. Steady-state concentrations are attained within 14 wely. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accu-mulation is predictable from single-dose pharmacokinetics. # steady state, the pharmacokinetics of aripiprazole are use-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, morphe and CVP2A4 CYP2D6 and CYP3A4.

inpiprazole is well absorbed, with peak plasma concentra-Suppravale is well absorbed, with peak plasma concerning has occurring within 3 to 5 hours; the absolute oral bio-reliability of the tablet formulation is 87%. ABILIFY can be administered with or without food. Administration of a Sing ABILIFY tablet with a standard high-fat meal did significantly affect the C_{max} or AUC of aripiprazole or its ative metabolite, dehydro-aripiprazole, but delayed T_{max} by a playment of the standard standard the dehydrohours for aripiprazole and 12 hours for dehydroripiprazole.

Distribution

Destruction The steady-state volume of distribution of aripiprazole fol-wring intravenous administration is high (404 L or 49 L/kg), indicating extensive extravascular distribution. a branching extensive extensive distribution at heapeutic concentrations, aripiprazole and its major peabolite are greater than 99% bound to serum proteins, pmarily to albumin. In healthy human volunteers adminprmany to automin. In neuron normal neuron series of the s

Metabolism and Elimination

Mabolism and Elimination Ampiprazole is metabolized primarily by three biotransfor-mation pathways: dehydrogenation, hydroxylation, and N-balkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is cata-ired by CYP3A4. Aripiprazole is the predominant drug coling in the systemic circulation. At steady state dehydrory motety in the systemic circulation. At steady state, dehydro arpiprazole, the active metabolite, represents about 40% of anipiprazole AUC in plasma.

approximately 8% of Caucasians lack the capacity to me-bolize CYP2D6 substrates and are classified as poor me-uvilizers (PM), whereas the rest are extensive metabolizrs (EM). PMs have about an 80% increase in aripiprazole eposure and about a 30% decrease in exposure to the active erosure 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 does of aripiprazole compared to EMs. Coadministration of BILFY (aripiprazole) with known inhibitors of CYP2D6, his quindine in EMs, results in a '112% increase in arip-granle plasma exposure, and dosing adjustment is needed is PECCAUTIONS: Drug-Drug Interactions). The mean dimention helicity are and the fourts and 146 hours for emination half-lives are about 75 hours and 146 hours for arpiprazole in EMs and PMs, respectively. Aripiprazole tes not inhibit or induce the CYP2D6 pathway.

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

Special Populations

in general, no dosage adjustment for ABILIFY is required in general, no double of a patient's age, gender, race, smoking status, mathe basis of a patient's age, gender, race, smoking status, benetic function, or renal function (see **DOSAGE AND AD** MINISTRATION: Dosage in Special Populations). The parmacokinetics of aripiprazole in special populations are described below.

Hepatic Impairment

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

Renal Impairment

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

Riderly

h formal single-dose pharmacokinetic studies (with arip-In normal sugge-cose pharmacontactic sources (which appendix given in a single dose of 15 mg), aripiprazole clear-nex was 20% lower in elderly (\geq 65 years) subjects com-ared to younger adult subjects (18 to 64 years). There was preu or younget autur subjects (10 to 04 years). Inere was no detectable age effect, however, in the population pharma-onisetic analysis in schizophrenia patients. Also, the phar-movimetics 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).

and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than mmen, and correspondingly, the apparent oral clearance of mpiprazole 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 Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of arip-iprazole, 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.

Based on studies utilizing human liver enzymes in vitro, aripiprazole is not a substrate for CYP1A2 and also does not Smoking ampiprazole is not a substrate for OTT in 2 and also uses 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 pharma-cokinetic 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.

other factors, like smoking, is unlikely. Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (e.g., carbamaze-pine) 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 phar-macokinetic interactions with drugs metabolized by cytomacokinetic interactions with drugs metabolized by cyto-chrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of arpiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextro-methorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **PRECAU-TIONS** Durage Durageting). TIONS: Drug-Drug Interactions).

Aripiprazole had no clinically important interactions with the following drugs:

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, de-creased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the C_{max} of aripipra zole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dos-age adjustment of aripinrazole is required when adminicage adjustment of arbitrazole is required when adminis-tered concomitantly with famotidine. Valproate: When valproate (500-1500 mg/day) and arip-

prazole (30 mg/day) were coadministered at steady state, prazole (so ingrazy) were coaunitistered at steady state, the C_{max} and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when ad-

ministered 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 the coses of infinite (1200-1000 mg/day) for 27 days which aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole ($C_{\rm max}$ 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. Aripipra way known to be dependent on CYP2Ds activity. Arripha-zole 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 arripiprazole.

auministered conconneanay with ampiprazole. 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 Normal-ized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of bights metabolism or metabolism of 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 no effect on the pharmacokinetics of a single zoring door of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when admin-istered concomitantly with aripiprazole.

Clinical Studies

The efficacy of ABILIFY (aripiprazole) in the treatment of The efficacy of ABLLIFY (ampiprazole) in the treatment of schizophrenia was evaluated in four short-term (4 and 6-week), placebo-controlled trials of acutely relapsed inpa-tients who predominantly met DSM-III/IV criteria for schizophrenia. Three of the four trials were able to distin-guish aripiprazole from placebo, but one study, the smallest, did not. Three of these studies also included an active con-

trol group consisting of either risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for comparison of ABILIFY and the active comparators.

a comparison of ABILIFY and the active comparators. In the three positive trials for ABILIFY, four primary meas-ures were used for assessing psychiatric signs and symp-toms. 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 PANSE positive active as whest of items in the The PANSS positive subscale is a subset of items in the PANSS that rates seven positive symptoms of schizophrenia ANSS that rates seven positive symptoms of schizophrenia (delusions, conceptual disorganization, hallucinatory behav-ior, 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, nassive anathetic withdrawal difficulty in obstact schizophrenia (biuntea affect, emotional windurawa, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, stereo-typed thinking). The Clinical Global Impression (CGI) as-sessment reflects the impression of a skilled observer, fully construct the market state of a skilled observer. familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

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

In a 4-week trial (n=404) comparing two fixed doses of ABLLFY (20 or 30 mg/day) and risperidone (6 mg/day) to placebo, both doses of ABLLFY 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 ABLLFY (10, 15, or 20 mg/day) to placebo, all three doses of ABLLFY were superior to placebo in the PANSS total score, PANSS positive subscale, and the PANSS negative subscale. subscale

subscale. In a fourth study, a 4-week trial (n=103) comparing ABILJFY 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 pri-mary outcomes for that trial. ABILJFY was only signif-eratly different compared to placebo in a responder analysis

mary outcomes for that that ABILIFY was only signifi-cantly 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 avidence in any shull that the higher deca 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 CLINI-CAL PHARMACOLOGY: Clinical Studies).

The long-term efficacy of aripiprazole in the treatment of the ingretine entrary of an input table in the treatment of schizophrenia has not been established. The physician who elects to use ABLLIFY for extended periods should periodi-cally 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)

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been re-ported 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 sta-tus, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine bhosphokinase. myoglobinuria (rhabdomyolysis), 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 exclude cases where the childran 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 tangitt heat starka durg four and arimary control partoxicity, heat stroke, drug fever, and primary central ner-

vous system pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not es-sential 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

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Abilify-Cont.

If a patient requires antipsychotic drug treatment after re-covery from NMS, the potential reintroduction of drug ther-apy 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 annetic movements may develop in patients treated with an-tipsychotic 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 anti-psychotic drug products differ in their potential to cause tar-dive dyskinesia is unknown. dive 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 the duration of treatment and the total commuters does 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, par-tially or completely, if antipsychotic treatment is withtially or completely, if antipsychotic treatment is with-drawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the under-lying 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 dyskinsia. Chronic antinsychotic treatment

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 ap-propriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment pro-ducing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed The need for continued treatment should be reassessed

The need for continued recenter was appear in a periodically. If signs and symptoms of tardive dyskinesia appear in a pa-tient on ABILIFY, drug discontinuation should be consid-ered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

PRECAUTIONS

General

Orthostatic Hypotension Aripiprazole may be associated with orthostatic hypo-tension, perhaps due to its al-adrenergic receptor antago-nism. 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 0.9%), and syncope (placebo 1%, aripiprazole 0.19%), or 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 arip-iprazole was not statistically different from placebo (14% among aripiprazole-treated patients, and 12% among Aripiprazole may be associated with orthostatic hypoamong aripiprazole-treated patients and 12% among

placebo-treated patients). Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infar-tion or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hy-povolemia, and treatment with antihypertensive medica-tions).

Seizure Seizures occurred in 0.1% (1/926) of aripiprazole-treated pa-tients 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 re-

Potential for Cognitive and Motor Impairment In short-term, placebo-controlled trials, somnolence was re-ported in 11% of patients on ABILIFY (aripiprazole) com-pared to 8% of patients on placebo; somnolence led to dis-continuation in 0.1% (1926) of patients on ABILIFY in short-term, placebo-controlled trials. Despite the relatively modest increased incidence of somnolence compared to pla-cebo, ABILIFY, like other antipsychotics, may have the po-tential to impair judgment, thinking, or motor skills. Pa-tients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them ad-versely. versely.

Body Temperature Regulation

Body Temperature Regulation Disruption of the body's ability to reduce core body temper-ature has been attributed to antipsychotic agents. Appropri-ate care is advised when prescribing aripiprazole for pa-tients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., ex-ercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or be-ing subject to debydrein ing subject to dehydration.

Information will be superseded by supplements and subsequent editions

Dysphagia Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly pa-tients, in particular those with advanced Alzheimer's de-mentia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneu-monia (see **PRECAUTIONS**: Use in Patients with Concom-itont Illness) itant 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 ABILEY should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of

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 Associ-ted 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 asso-ciated 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 follow-ing the discontinuation of ABLIIFY 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 \geq 5% and having a greater incidence than placebo in this study were accidental injury, somnolence, and bronchitis. Eight percent of the ABILIFY treated patients. In a small pilot, open-label, ascend-ing-dose cohort study (n=30) in elderly patients with dementia, ABILIFY was associated in a dose-related fash-ion with somnolence. The safety and efficacy of ABILIFY in the treatment of na-

ion with somnolence. The safety and efficacy of ABILIFY in the treatment of pa-Ine satety and emcacy of ABILIFY in the treatment of pa-tients with psychosis associated with dementia have not been established. If the prescriber elects to treat such pa-tients with ABILIFY, vigilance should be exercised, partic-ularly for the emergence of difficulty swallowing or exces-sive sommolence, which could predispose to accidental injury or assniration injury or aspiration.

injury or aspiration. Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses (see CLINICAL PHARMA-COLOGY: Special Populations: Renal Impairment and He-patic Impairment) is limited. ABILIFY

patic impairment) is limited. ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial in-farction or unstable heart disease. Patients with these diag-noses 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 judg-ment, thinking, or motor skills, patients should be cau-tioned about operating hazardous machinery, including au-tomobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely. Pregnarcy Pregnancy

Patients should be advised to notify their physician if they rauents should be advised to notify their physician if they become pregnant or intend to become pregnant during ther-apy 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 attention.

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.

avoiding overneating and denymercon. 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 Potential for Other Drugs to Affect ABILITY Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of arip-iprazole with inhibitors or inducers of these enzymes, or other factore like sending is unlikely

iprazole with inhibitors or inducer's 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., carbamaze-pine) 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 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 metaboli increased the AUC of aripiprazole and its active metabolie by 65% and 77%, respectively. The effect of a higher keto-conazole dose (400 mg/day) has not been studied. When con-comitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half offis normal dose. Other strong inhibitors of CYP3A4 (itraconi-zole) would be expected to have similar effects and need similar dose reductions; weaker inhibitors (crythromycin, grapefruit uice) have not been studied. When the CYP3A4

similar dose reductions; weaker inhibitors (erythromytei, grapefruit juice) have not been studied. When the CYF344 inhibitor is withdrawn from the combination therapy, arp-prazole dose should then be increased. *Quinidine*: Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), apo-tent inhibitors of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, de hydro-aripiprazole, by 35%. Aripiprazole dose should be re-duced to one-half of its normal dose when concomitant ad-ministration of quinidine with aripiprazole cocurs. Other significant inhibitors of CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should be recombination therapy, aripiprazole dose should then be increased.

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

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

(see CLINICAL PHARMACOLOGY, big she interactions).
Potential for ABILIFY to Affect Other Drugs
Aripiprazole is unlikely to cause clinically important plarmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In in vivo studies, 10- to 30-mg/dg doses of aripiprazole had no significant effect on metabolism by CYP2C19 (omeprazole, warfarin), and CYP3C4 (deximation of the context of the c

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis Lifetime carcinogenicity studies were conducted in ICB mice and in Sprague-Dawley (SD) and F344 rats. Aripin-zole was administered for 2 years in the diet at doses of 1, 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 maximu recommended human dose (MRHD) based on mg/m², re-spectively). 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/m². Aripiprazole did not induce tumor in male mice or rats. In female mice, the incidences of pin-itary gland adenomas and mammary gland adenocarino-mas and adenoacanthomas were increased at dietary dose in male mice or rats. In female mice, the incidences of pin-itary gland adenomas and mammary gland adenoaratios 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 human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m²). In female rats, the incidence of mammary gland day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m²); and the incidences of adrenocortical carcinomas and combined adrenocutal 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/m²). Proliferative changes in the pituitary and mammary glasd of rodents have been observed following chronic administr-tion of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured 13-week dietary study at the doses associated with mam-mary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mamary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown. Mutaneensis

mediated endocrine tumors in rodents is unknow

Mutagenesis

The mutagenic potential of aripiprazole was tested in the in I ne mutagenic potential of aripiprazole was tested in the *n 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 aber-tion assay in Chinese hamster lung (CHL) cells, the *in vico* micromutane correct micro and the *in vico* and the *in vico* tion assay in Chinese hamster lung (CHL) cells, the *in woo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Arripiprazole and a metabolite (23-DCPP) were clastogenic in the *in vitro* chromosomal ate-ration assay in CHL cells with and without metabolite adi-vation. 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

PRODUCT INFORMATION

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

ale rats were treated with oral doses of 2, 6, and 20 mg remarks were treated with one does of 2, 6, and 20 mg/ gidsy (0.6, 2, and 6 times the maximum recommended hu-man dose (MRHD) on a mg/m² basis) of aripiprazole from 2 weks prior to mating through day 7 of gestation. Estrus releirregularities and increased corpora lutea were seen at I doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg, and dereased fetal weight was seen at 20 mg/kg. Male rats were treated with oral doses of 20, 40, and 60 mg/

igiday (6, 13, and 19 times the MRHD on a mg/m² basis) of guy (o, to, and is onlies to all of an angle on a signification of the set of rment of fertility was seen.

Pregnancy Category C

In animal studies, aripiprazole demonstrated developmen a toxicity, including possible teratogenic effects in rats and abhite

Pagnant rats were treated with oral doses of 3, 10, and 0 mg/kg/day (1, 3, and 10 times the maximum recom-mended human dose [MRHD] on a mg/m² basis) of aripipranie during the period of organogenesis. Gestation was sightly prolonged at 30 mg/kg. Treatment caused a slight day in fetal development, as evidenced by decreased fetal eay in retai development, as evidenced by decreased retai wight (30 mg/kg), undescended testes (30 mg/kg), and de-igned skeletal ossification (10 and 30 mg/kg). There were no inverse effects on embryofietal or pup survival. Delivered desping had decreased bodyweights (10 and 30 mg/kg), and acressed incidences of hepatodiaphragmatic nodules and inpragmatic hernia at 30 mg/kg (the other dose groups are not examined for these findings). (A low incidence of inpragmatic hernia was also seen in the fetuses exposed /kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance allo and 30 mg/kg and imparted reproductive performance decreased fertility rate, corpora lutea, implants, and live knues, and increased post-implantation loss, likely medi-ned through effects on female offspring) was seen at 30 mg/kg, breve 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 10 mg/kg/day (2, 3, and 11 times human exposure at WRHD based on AUC and 6, 19, and 65 times the MRHD used on mg/m²) of aripiprazole during the period of orga-ngenesis. Decreased maternal food consumption and inmased abortions were seen at 100 mg/kg. Treatment assed increased fetal mortality (100 mg/kg), decreased fe-al weight (30 and 100 mg/kg), increased incidence of skelsal abnormality (fused sternebrae at 30 and 100 mg/kg) miminor skeletal variations (100 mg/kg).

mastudy 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 signal dasis) of aripiprazole perinatally and postnatally from day 17 of gestation through day 21 postpartum), aght maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and de-grasses in pup weight (persisting into adulthood) and sural were seen at this dose.

There are no adequate and well-controlled studies in preg-sant women. It is not known whether aripiprazole can an women it is not known whether arphyrazole can arge fetal harm when administered to a pregnant woman ran affect reproductive capacity. Arphyrazole should be sed during pregnancy only if the potential benefit out-regis the potential risk to the fetus. Ishor and Delivery

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

Nursing Mothers

inpiprazole was excreted in milk of rats during lactation. It snotknown whether aripiprazole or its metabolites are ex-meted in human milk. It is recommended that women resiving aripiprazole should not breast-feed.

Mediatric Use Methy and effectiveness in pediatric and adolescent paents have not been established.

Reliatric Use

the 552 patients treated with aripiprazole in premar-ting clinical trials, 659 (12%) were \geq 65 years old and 525 %) were \geq 75 years old. The majority (91%) of the 659 pawere diagnosed with dementia of the Alzheim

Enzobe-controlled studies of aripiprazole in schizophrenia and include sufficient numbers of subjects aged 65 and The induce sufficient infinites of subjects aged to any more to determine whether they respond differently from more subjects. There was no effect of age on the pharma-metrics of a single 15-mg dose of aripiprazole. Aripipra-de clearance was decreased by 20% in elderly subjects Howears) compared to younger adult subjects (18 to 64 s), but there was no detectable effect of age in the pop-ion pharmacokinetic analysis in schizophrenia patients. ndies of elderly patients with psychosis associated with themer's disease, have suggested that there may be a difrent tolerability profile in this population compared to onger patients with schizophrenia (see **PRECAUTIONS:** *is in Patients with Concomitant Illness*). The safety and acy of ABILIFY (aripiprazole) in the treatment of pa-ts with psychosis associated with Alzheimer's disease us not been established. If the prescriber elects to treat an patients with ABILIFY, vigilance should be exercised.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 5592 natients 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 re-ported 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 inci-dence 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 pro-vide the prescribing physician with some basis for estimat-ing 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 Treat-ment in Short-Term, Placebo-Controlled Trials

Overall, there was no difference in the incidence of discontinuation due to adverse events between aripiprazoletreated (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 Pla-cebo 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 $\geq 2 \text{ mg/day}$) 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

Percentag Body System Adverse Event	ge of Patients Repor Aripiprazole (n=926)	rting Event ^a Placebo (n=413)
Body as a Whole	Same Pice	dia a
Headache	32	25
Asthenia	7	5
Fever	2	1.1.1
Digestive System		
Nausea	14	10
Vomiting	12	- 7
Constipation	10	8
Nervous System	 and the logical 	
Anxiety	25	24
Insomnia	24	19
Lightheadedness	11	1. 20. 7
Somnolence	11 201200	8
Akathisia	10	7
Tremor	3	2
Respiratory System		
Rhinitis	4	3
Coughing	3	2
Skin and Appendage:	s	
Rash	6	5
Special Senses		
Blurred vision	3	1 1 2

Events reported by at least 2% of patients treated with aripiprazole, except the following events, which had an in-cidence equal to or less than placebo: abdominal pain, accidental injury, back pain, dental pain, dyspepsia, diardry mouth, myalgia, agitation, psychosis, rhea,

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 In-voluntary 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 aripipra-zole/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 In sort-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 27% of body weight [aripiprazole (8%) compared to placebo (3%)]. The following table provides the weight change re-sults from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of \geq 7% of body weight relative to baseline, categorized by BMI at baseline:

Table 2: Weight Change Results Categorized by BMI at

	Das	calle	
Mean	<u>BMI <23</u>	BMI 23-27	<u>BMI >27</u>
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 incre 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 intro-duction 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 2. Ingular during any prase 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 AD-VERSE 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 impor-tant 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 rain, neck rigidy: In/requent – pel-vic pain, suicide attempt, face edema, malaise, photosensi-tivity, arm rigidity, jaw pain, chills, bloating, jaw tightness, enlarged addomen, 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

Consult 2004 PDR® supplements and future editions for revisions

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Abilify-Cont.

Cardiovascular System: Frequent - hypertension, tachy-cardia, hypotension, bradycardia; Infrequent - palpitation, hemorrhage, myocardiai infarction, prolonged QT interval, cardiac arrest, atrial fibrillation, heart failure, AV block, myocardial ischemia, phlebitis, deep vein thrombosis, an-gina pectoris, extrasystoles; *Rare* – vasovagal reaction, car-diomegaly, atrial flutter, thrombophlebitis.

Digestive System: Frequent - anorexia, nausea and vomit-ing; Infrequent - increased appetite, gastroenteritis, dyshttp://gradience.gastoenceris, togshoenceris, yas-phagia, flaulence, gastroitis, tooth caries, gingivitis, hemo-rhoids, gastroesophageal reflux, gastrointestinal hemorrhage, periodontal abscess, tongue edema, fecal in-continence, colitis, rectal hemorrhage, stomatitis, mouth ul-er, cholecystitis, fecal impaction, oral moniliasis, cholelithi-tis methods and a store and a store and a store and a store in the store and a store and a store and a store and a store in the store and a store a asis, eructation, intestinal obstruction, peptic ulcer: Rare esophagitis, gum hemorrhage, glossitis, hematemesis, me-lena, duodenal ulcer, cheilitis, hepatitis, hepatomegaly, pan-

esopitaguis, guin neutoringe, guossius, nenacemens, meracemens, meracemens, meracemens, meracemens, meracemens, languaguis, meracemens, languaguis, meracemens, languaguis, mic reaction.

Intersection: Musculoskeletal System: Frequent – muscle cramp; Infre-quent – arthralgia, bone pain, myasthenia, arthritis, arthro-sis, muscle weakness, spasm, bursitis; Rare – nhabdomyol-ysis, tendonitis, tenosynovitis, rheumatoid arthritis, myopathy.

Nervous System: Frequent - depression, nervousness, in-creased 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, dyski-nesia, hypersomnia, vertigo, dysarthria, tardive dyskinesia, ataxia, impersonnia, verigo, uysartina, tarure dyskinesia, ataxia, impaired memory, stupor, increased libido, amnesia, cerebrovascular accident, hyperactivity, depersonalization, hypokinesia, restless leg, myoclonus, dysphoria, neuropa-thy, increased reflexes, slowed thinking, hyperkinesia, hy-peresthesia, hypotonia, oculogyric crisis; Rare – delirium, euphoria, buccoglossal syndrome, akinesia, blunted affect, decreased consciousness, incoordination, cerebral ischemia, decreased reflexes, obsessive thought, intracranial hemmorhage.

mornage. Respiratory System: Frequent – dyspnea, pneumonia; In-frequent – asthma, epistaxis, hiccup, laryngitis; Rare – he-moptysis, aspiration pneumonia, increased sputum, dry nasal passages, pulmonary dema, pulmonary embolism, hypoxia, respiratory failure, apnea.

hypoxia, respiratory failure, apnea. Skin and Appendages: Frequent – dry skin, pruritis, sweating, skin ulcer; Infrequent – acne, vesiculobullous rash, eczema, alopecia, psoriasis, seborrhea; Rare – maculo-papular rash, exfoliative dermatitis, urticaria. Special Senses: Frequent – conjunctivitus, ear pain; Infre-quent – dry eye, eye pain, tinnitus, otitis media, cataract, altered taste, blepharitis; Rare – increased lacrimation, fre-quent blinking, ottis externa, amblyopia, deafness, diplo-tion with bingeness. pia, eye hemorrhage, photophobia. Urogenital System: Frequent – urinary incontinence; In

frequent – cystitis, urinary frequency, leukorrhea, urinary retention, hematuria, dysuria, amenorrhea, abnormal ejac-ulation, vaginal hemorrhage, vaginal moniliasis, kidney failure, uterus hemorrhage, menorrhagia, albuminuria, kid-ney calculus, nocturia, polyuria, urinary urgency; Rare – bréast 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, with-drawal 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 mar-keted. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be ob-served 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 arip-iprazole was identified in seven patients. In the two pa-

Information will be superseded by supplements and subsequent editions

tients 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 hos-pital 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 inession of ATUAN® 18-month-old child, with concomitant ingestion of ATTVAN®

(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 prolon-gation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxy-genation 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 (arip-

iprazole), an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Admin-istration 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 ef-

fect of hemodialysis in treating an overdose with aripipra-zole, 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 concom-itantly with potential CYP3A4 inhibitors: When concomi-When concomitant administration of ketoconazole with aripiprazole oc-curs, 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.

Increased. Dosage adjustment for patients taking aripiprazole concom-itantly with potential CYP2D6 inhibitors: When concomi-tant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole oc-curs, 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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a Wyeth-Ayerst Company. Dosage adjustment for patients taking potential CYP3A4 in-ducers: 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.

arbitrazole 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 deter-mine the need for maintenance treatment.

Switching from Other Antipsychotics There are no systematically collected data to specifically ad-dress switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant admin-istration 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 mon-keys did not reveal evidence of retinal degeneration. Addi-tional 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 fol-lowing strengths and packages.

PHYSICIANS' DESK REFERENCE®

The 5-mg ABILIFY table	ts are blue, modified rectangular
toblets debessed on one	at 1 - mith #A 007" and 45"
Bottles of 30	NDC 59148-007-33 NDC 59148-007-33
Blister of 100	NDC 59148-007-35
The 10-mg ADILIF I tabl	ets are pink, modified recompa-
lar tablets, debossed on a	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 tabl	ets are yellow, round tablets, de-
bossed 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 tabl	ets are white, round tablets, de-
bossed on one side with '	"A-010" and "20".
Bottles of 30	NDC 59148-010-13
Blister of 100	NDC 59148-010-13 NDC 59148-010-35
The 30-mg ABILIFY tab	lets are pink, round tablets, de-
bossed on one side with '	
Blister of 100	NDC 59148-011-13 NDC 59148-011-35
Storage	the state of the printing of
	rsions permitted to 15-30° C (59-
6° F) [see USP Controlled	Room Temperaturel.
Jarketed by Otsuka Amer	rica Pharmaceutical, Inc, Rock-
ille, MD 20850 USA	NELLING ALL AND
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	Pharmaceutical Co, Ltd, Tokyo,
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PLETAL®

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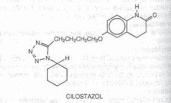
(cilostazol) (sil-OS-tah-zol) Tablets

CONTRAINDICATION

CONTRAINDIGATION Cilostazol and several of its metabolites are inhibitors of phosphodiesterase III. Several drugs with this pharma cologic effect have caused decreased survival compared to placebo in patients with class III-IV congestive hear 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 cilostazel Coold 27, 502, and its molecular weight is 369.47. Cilostant is 6-[4-(1-cyclohexy]-1H-tetrazol-5-y])butoxy]-3,4-dihydro 2(1H)-quinolinone, CAS-73963-72-1. The structural formula is:



Cilostazol occurs as white to off-white crystals or as a crytalline powder that is slightly soluble in methanol and et-anol, 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 de bossed tablets. Each tablet, in addition to the active ingredient, contains the following inactive ingredients: carboy methylcellulose calcium, corn starch, hydroxypropil methylcellulose 2910, magnesium stearate, and microrys talline cellulos

CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism of the effects of PLETAL on the symp The internation of the effects of PLETAD on the synthesis of intermittent claudication is not fully understood. PLE TAL and several of its metabolites are cyclic AMP (cAMP) phosphodiesterase III inhibitors (PDE III inhibitors) inhibiiting 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, ar achidonic acid, epinephrine, and shear stress. Effects on dr