IN THE UNITED STATES DISTRICT COURT
DISTRICT OF ALASKA

UNITED STATES OF AMERICA *Ex rel.* Law Project for Psychiatric Rights, an Alaskan non-profit corporation, Plaintiff, vs. OSAMU H. MATSUTANI, MD, *et al*., Defendants.	)	**CIVIL ACTION NO. 3:09-CV-00080-TMB**

TABLE OF CONTENTS FOR EXHIBITS TO PSYCHRIGHTS' MOTION FOR PRELIMINARY AGAINST DEFENDANTS HOGAN AND STREUR

Department of Justice

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Justice Department Announces Largest Health Care Fraud Settlement in Its History

Pfizer to Pay $2.3 Billion for Fraudulent Marketing

WASHINGTON – American pharmaceutical giant Pfizer Inc. and its subsidiary Pharmacia & Upjohn Company Inc. (hereinafter together "Pfizer") have agreed to pay $2.3 billion, the largest health care fraud settlement in the history of the Department of Justice, to resolve criminal and civil liability arising from the illegal promotion of certain pharmaceutical products, the Justice Department announced today.

Pharmacia & Upjohn Company has agreed to plead guilty to a felony violation of the Food, Drug and Cosmetic Act for misbranding Bextra with the intent to defraud or mislead. Bextra is an anti-inflammatory drug that Pfizer pulled from the market in 2005. Under the provisions of the Food, Drug and Cosmetic Act, a company must specify the intended uses of a product in its new drug application to FDA. Once approved, the drug may not be marketed or promoted for so-called "off-label" uses – *i.e.*, any use not specified in an application and approved by FDA. Pfizer promoted the sale of Bextra for several uses and dosages that the FDA specifically declined to approve due to safety concerns. The company will pay a criminal fine of $1.195 billion, the largest criminal fine ever imposed in the United States for any matter. Pharmacia & Upjohn will also forfeit $105 million, for a total criminal resolution of $1.3 billion.

In addition, Pfizer has agreed to pay $1 billion to resolve allegations under the civil False Claims Act that the company illegally promoted four drugs – Bextra; Geodon, an anti-psychotic drug; Zyvox, an antibiotic; and Lyrica, an anti-epileptic drug – and caused false claims to be submitted to government health care programs for uses that were not medically accepted indications and therefore not covered by those programs. The civil settlement also resolves allegations that Pfizer paid kickbacks to health care providers to induce them to prescribe these, as well as other, drugs. The federal share of the civil settlement is $668,514,830 and the state Medicaid share of the civil settlement is $331,485,170. This is the largest civil fraud settlement in history against a pharmaceutical company.

As part of the settlement, Pfizer also has agreed to enter into an expansive corporate integrity agreement with the Office of Inspector General of the Department of Health and Human Services. That agreement provides for procedures and reviews to be put in place to avoid and promptly detect conduct similar to that which gave rise to this matter.

Whistleblower lawsuits filed under the *qui tam* provisions of the False Claims Act that are pending in the District of Massachusetts, the Eastern District of Pennsylvania and the Eastern District of Kentucky triggered this investigation. As a part of today's resolution, six whistleblowers will receive payments totaling more than $102 million from the federal share of the civil recovery.

The U.S. Attorney's offices for the District of Massachusetts, the Eastern District of Pennsylvania, and the Eastern District of Kentucky, and the Civil Division of the Department of Justice handled these cases. The U.S. Attorney's Office for the District of Massachusetts led the criminal investigation of Bextra. The investigation was conducted by the Office of Inspector General for the Department of Health and Human Services (HHS), the FBI, the Defense Criminal Investigative Service (DCIS), the Office of Criminal Investigations for the Food and Drug Administration (FDA), the Veterans' Administration's (VA) Office of Criminal Investigations, the Office of the Inspector General for the Office of Personnel Management (OPM), the Office of the Inspector General for the United States Postal Service (USPS), the National Association of Medicaid Fraud Control Units and the offices of various state Attorneys General.

"Today's landmark settlement is an example of the Department of Justice's ongoing and intensive efforts to protect the American public and recover funds for the federal treasury and the public from those who seek to earn a profit through fraud. It shows one of the many ways in which federal government, in partnership with its state and local allies, can help the American people at a time when budgets are tight and health care costs are increasing," said Associate Attorney General Tom Perrelli. "This settlement is a testament to the type of broad, coordinated effort among federal agencies and with our state and local partners that is at the core of the Department of Justice's approach to law enforcement."

"This historic settlement will return nearly $1 billion to Medicare, Medicaid, and other government insurance programs, securing their future for the Americans who depend on these programs," said Kathleen Sebelius, Secretary of Department of Health and Human Services**.** "The Department of Health and Human Services will continue to seek opportunities to work with its government partners to prosecute fraud wherever we can find it. But we will also look for new ways to prevent fraud before it happens. Health care is too important to let a single dollar go to waste."

"Illegal conduct and fraud by pharmaceutical companies puts the public health at risk, corrupts medical decisions by health care providers, and costs the government billions of dollars," said Tony West, Assistant Attorney General for the Civil Division. "This civil settlement and plea agreement by Pfizer represent yet another example of what penalties will be faced when a pharmaceutical company puts profits ahead of patient welfare."

"The size and seriousness of this resolution, including the huge criminal fine of $1.3 billion, reflect the seriousness and scope of Pfizer's crimes," said Mike Loucks, acting U.S. Attorney for the District of Massachusetts. "Pfizer violated the law over an extensive time period. Furthermore, at the very same time Pfizer was in our office negotiating and resolving the allegations of criminal conduct by its then newly acquired subsidiary, Warner-Lambert, Pfizer was itself in its other operations violating those very same laws. Today's enormous fine demonstrates that such blatant and continued disregard of the law will not be tolerated."

"Although these types of investigations are often long and complicated and require many resources to achieve positive results, the FBI will not be deterred from continuing to ensure that pharmaceutical companies conduct business in a lawful manner," said Kevin Perkins, FBI Assistant Director, Criminal Investigative Division.

"This resolution protects the FDA in its vital mission of ensuring that drugs are safe and effective. When manufacturers undermine the FDA's rules, they interfere with a doctor's judgment and can put patient health at risk," commented Michael L. Levy, U.S. Attorney for the Eastern District of Pennsylvania. "The public trusts companies to market their drugs for uses that FDA has approved, and trusts that doctors are using independent judgment. Federal health dollars should only be spent on treatment decisions untainted by misinformation from manufacturers concerned with the bottom line."

"This settlement demonstrates the ongoing efforts to pursue violations of the False Claims Act and recover taxpayer dollars for the Medicare and Medicaid programs," noted Jim Zerhusen, U.S. Attorney for the Eastern District of Kentucky.

"This historic settlement emphasizes the government's commitment to corporate and individual accountability and to transparency throughout the pharmaceutical industry," said Daniel R. Levinson, Inspector General of the United States Department of Health and Human Services. "The corporate integrity agreement requires senior Pfizer executives and board members to complete annual compliance certifications and opens Pfizer to more public scrutiny by requiring it to make detailed disclosures on its Web site. We expect this agreement to increase integrity in the marketing of pharmaceuticals."

"The off-label promotion of pharmaceutical drugs by Pfizer significantly impacted the integrity of TRICARE, the Department of Defense's healthcare system," said Sharon Woods, Director, Defense Criminal Investigative Service. "This illegal activity increases patients' costs, threatens their safety and negatively affects the delivery of healthcare services to the over nine million military members, retirees and their families who rely on this system. Today's charges and settlement demonstrate the ongoing commitment of the Defense Criminal Investigative Service and its law enforcement partners to investigate and prosecute those that abuse the government's healthcare programs at the expense of the taxpayers and patients."

"Federal employees deserve health care providers and suppliers, including drug manufacturers, that meet the highest standards of ethical and professional behavior," said Patrick E. McFarland, Inspector General of the U.S.

Office of Personnel Management. "Today's settlement reminds the pharmaceutical industry that it must observe those standards and reflects the commitment of federal law enforcement organizations to pursue improper and illegal conduct that places health care consumers at risk."

"Health care fraud has a significant financial impact on the Postal Service. This case alone impacted more than 10,000 postal employees on workers' compensation who were treated with these drugs," said Joseph Finn, Special Agent in Charge for the Postal Service's Office of Inspector General. "Last year the Postal Service paid more than $1 billion in workers' compensation benefits to postal employees injured on the job."

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09-900

Revision: HCFA-PM-91-4 (BPD) OMB No. 0938-
AUGUST 1991

STATE PLAN UNDER TITLE XIX OF THE SOCIAL SECURITY ACT
MEDICAL ASSISTANCE PROGRAM

State/Territory: ALASKA

Citation

42 CFR
430.10

As a condition for receipt of Federal funds under title XIX of the Social Security Act, the

Department of Health and Social Services
(Single State Agency)

submits the following State plan for the medical assistance program, and hereby agrees to administer the program in accordance with the provisions of this State plan, the requirements of titles XI and XIX of the Act, and all applicable Federal regulations and other official issuances of the Department.

11375 DATA REQUIREMENTS

The minimum data element file requirements for systems approval derive from State plan requirements and Federal reporting requirements. Data elements related to services not covered in the State plan need not be included.

Claim format and content varies depending upon the type of provider that submits a claim and individual State plan requirements.

NOTE: Subtitle F of Public Law 104-191 mandates that the Secretary of the Department of Health and Human Services adopt a wide range of national standards for the electronic exchange of health information. Standards are to be adopted for: 1) electronic transactions and data elements, 2) code sets, 3) unique health identifiers for individuals, providers, health plans, and employers, 4) security of health information, and 5) electronic signatures. The recommended standards for various types of standards mandated under Public Law 104-191 will be made available for public comment via Notices of Proposed Rulemaking in the Federal Register. Once standards are published as Final Rules in the Federal Register, States and all health related providers must implement standards within 2 years from the Federal Register publication date. The final standards will supersede any/all standards currently in place for electronic transactions and data elements.

The Uniform Hospital Discharge Data Set (UHDDS), developed through the National Committee on Vital and Health Statistics (NCVHS) and required by HHS departmental policy, effective January 1, 1975, and which meets current PRO requirements of §11205, contains, for hospital service only, discharge data as a file requirement and is identified in this section as:

* UHDDS as well as MMIS requirement
** UHDDS requirement only

The following data elements contained in the systems files are minimal and not exclusive requirements for source and use within the MMIS.

1. Recipient Identification Number:
   A number that uniquely identifies an individual eligible for Medicaid benefits.

*2. Recipient Social Security Number (SSN):
   The number used by SSA throughout a wage earner's lifetime to identify earnings under the Social Security program.

   For newborns and children not having a SSN but covered under Medicaid use No. 1 above to identify these eligibles.

3. Recipient Social Security Claim Number:
   The number assigned to an individual by the SSA under which monthly cash benefits (and Medicare benefits) are paid or eligibility is established.

4. Recipient's Name:
   The name of the recipient.

*5. Recipient's Address:
The address of the recipient.

*6. Recipient's Date of Birth:
The date of birth of the recipient.

7. Recipient's Race Code:
a. The racial origin of the recipient
** b. Race/Ethnic
White, Black, Hispanic, Asian/Pacific Islander, American/Indian/Alaska Native, and other

*8. Recipient's Sex Code:
The sex of the recipient.

9. Recipient's Aid Category:
The statutory category of public assistance, SSI or State supplementary payment under which a recipient is eligible for Medicaid benefits.

10. Gross Family Income:
The monthly gross income for the family of which this recipient is a member.

11. Family Size:
The number of persons in the family of which this recipient is a member.

12. Eligibility Beginning Date:
A date that begins a period in which a recipient was certified as eligible to receive Medicaid benefits.

13. Eligibility Ending Date:
A date concluding a period in which a recipient is eligible to receive Medicaid benefits.

14. Third Party Liability Code:
a. A code indicating availability to a recipient of potential third party resources.
** b. Expected Principal Source of Payment
(1) Self-pay
(2) Workmen's Compensation
(3) Medicare
(4) Medicaid
(5) Maternal and Child Health
(6) Other Government Payments
(7) Blue Cross
(8) Insurance Companies
(9) No charge (free, charity, special research, or teaching)
(10) Other

15. Buy-In Status Code:
The code indicating a recipient's status with respect to the Medicare Buy- In Program.

16. Recipient Exception Indicator:
A code indicating that all claims for a given recipient are to be manually reviewed prior to payment.

17. Money Payment Code:
A code indicating whether or not the recipient is currently receiving cash assistance.

18. Medicare Type Code:
A code indicating whether the recipient is covered by Medicare, and, if so, whether he/she has Hospital Insurance Benefits (Part A) and/or Supplementary Medical Insurance Benefits (Part B).

19. Buy-In Eligibility Date:
The date from which the recipient is eligible for the Medicare Buy-In Program.

20. Buy-In Premium Date:
The date associated with a Buy-In premium amount.

21. Buy-In Premium Amount:
The amount of money the State pays to HCFA each month per recipient for Buy-In coverage.

22. SSA-Information Exchange Code:
A code scheme consisting of various numerical codes which describe situations that can occur at SSA or at the State level.

23. Recipient's Eligibility Certification Date:
Date recipient was certified as eligible for public assistance, supplemental security income or State supplemental benefits.

24. Recipient's Location Code:
The geographic or geopolitical subdivision of a State in which the recipient resides.

25. Medicaid Premium Amount:
A recurring premium paid by medically needy individuals before they can receive Medicaid services. The amount of the fee is based upon the number of persons in the family and the gross family income.

26. Medicaid Enrollment Fee Amount:
A one-time enrollment fee paid by medically needy individuals before they can receive Medicaid services. The amount of the fee is based on the number of persons in the family and the gross family income.

27. Medicaid Deductible Amount:
The annual (or other period) amount which the recipient must pay toward the cost of medical services before Medicaid will begin to pay.

28. Date of Death:
The date of a recipient's death as indicated in the Social Services or SSI file after an official notice of death has been received.

29. Provider Number (State):
A unique number assigned by the State to each participating provider of services.

30. Provider Name:
The name of the provider of Medicaid services as used on official State records.

31. Provider Address:
The mailing address of the provider.

32. Provider Pay to Address:
The address to which Medicaid payments to a provider are sent.

33. Provider Type:
A code indicating the classification of the provider rendering health and medical services as approved under the State Medicaid plan.

34. Provider Beginning Date of Service:
A date beginning a period in which the provider was authorized to receive Medicaid payments.

35. Provider Ending Date of Service:
A date concluding a period in which the provider is authorized Medicaid payments for services rendered.

36. Provider Group Number:
The number assigned to the group practice of which an individual provider is a member.

37. Provider Type of Practice Organization:
A code identifying the organizational structure of a provider's practice.

38. Provider Employer Identification Number:
The number assigned to an employer by the Internal Revenue Service for tax reporting purposes.

39. Provider Social Security Number:
The number assigned to an individual by SSA.

*40. Medicare Provider Number:
The identification number assigned to a Medicare provider by HCFA (provider means any individual or entity furnishing Medicaid services under a provider agreement with the Medicaid agency (Reference 42 CFR 430.l).

41. Provider Year End Date:
The calendar date on which the provider's fiscal year ends.

42. Provider Specialty Code:
A code used to indicate the medical specialty of a physician.

43. Provider Exception Indicator:
A code indicating that all claims from a given provider are to be manually reviewed prior to payment.

44. Provider Credit Balance Amount:
The amount of money the Medicaid program owes a provider.

45. Provider Credit Balance Date:
The processing date on which the last amount was entered in the Provider Credit Balance amount.

46. Out-of-State Provider Code:
A code indicating that the provider is located out of State.

47. Per Diem Rate:
The payment amount for each day of care in an institution reimbursed on a per diem basis.

48. Percent-of-Charges Factor:
The percent of a provider's charges that constitutes payment for certain categories of service.

49. Rate Effective Date:
The effective date of the accompanying per diem rate or percent-of-charges factor.

50. Provider Location Code:
The geographic or geopolitical subdivision in which the provider's place of business is located.

51. Provider Enrollment Status Code:
A code indicating a provider's certification status with respect to the Medicaid program.

52. Provider Enrollment Status Date:
The effective date of the accompanying provider enrollment status code.

53. Provider Group Name and Address:
The name and mailing address of the provider group.

54. Transaction Control Number:
A unique number identifying each claim transaction received.

55. Category of Service:
A code defining the category of service rendered (e.g., general inpatient, pharmacy, physician, home health).

56. Laboratory, Medicare Certified Indicator:
A code indicating that a laboratory is approved as meeting the requirements for participation in Medicare.

57. Laboratory Service Authorized Code:
A code indicating the services/procedures that a laboratory which meets the requirements for participation in Medicare is authorized to perform.

*58. Physician Identification:
a. Attending Physician Number
The provider number of the physician attending an inpatient in a hospital, nursing home, or other institution.

This is the physician primarily responsible for the care of the patient from the beginning of this institutional episode.

**b. Operating Physician
This is the physician who performed the principal procedure. See Data Element No. 87 below, for definition of principal procedure.

59. Referring Physician Number:
The provider number of the physician referring a recipient to another practitioner or provider.

60. Prescribing Physician Number:
The provider number of the physician issuing a prescription.

*61. Principal Diagnosis Code:
a. The diagnosis code for the principal condition requiring medical attention.

**b. The condition established after study to be chiefly responsible for causing the patient's admission to the hospital for care for the current hospital stay. (HCFA requires the acceptance of ICD-9-CM coding.)

62. Other Diagnosis Code:
a. The diagnosis code of any condition other than the principal condition which requires supplementary medical treatment.

**b. Conditions (up to four) other than the principal condition that coexisted at the time of admission, or developed subsequently, which affected the treatment received and/or the length of stay. Exclude diagnoses that relate to an earlier episode which have no bearing on this hospital stay. (HCFA requires the acceptance of ICD-9-CM coding.)

*63. Admission Date:
The date a recipient was admitted to a medical institution.

64. Beginning Date of Service:
The date upon which the first service covered by a claim was rendered. If a claim is for one service only (e.g., a prescription), this is the only service date.

65. Ending Date of Service:
The date upon which the last service covered by a claim was rendered.

*66. Discharge Date:
The formal release of an inpatient from a hospital.

67. Place of Service:
A code indicating where a service was rendered by a provider.

*68. Patient Number:
Any number assigned by a provider to a recipient or claim for reference purposes, such as a medical record number.

69. Patient Status:
A code indicating the patient's status on the last date of service covered by an institutional claim.

70. Total Claim Charge:
The sum of all charges associated with an individual claim.

71. Units of Service:
A quantitative measure of the services rendered to, or for, a recipient (e.g., days, visits, miles, injections).

72. Third Party Payment Amount:
The amount of payment applied toward a claim by third party sources.

73. Medicare Cash Deductible Amount:
The unmet Medicare deductible subject to payment by Medicaid.

74. Medicare Blood Deductible Amount:
The unmet Medicare deductible for blood subject to payment by Medicaid.

75. Medicare Coinsurance Charge:
The Medicare coinsurance amount subject to payment by Medicaid.

76. Medicare Reasonable Charge:
Payment amount recognized as the reasonable charge for Medicare.

77. Medicaid Co-Payment Amount:
The portion of the claim charge which the recipient must pay, called coinsurance when expressed as a percentage of the payment amount.

78. Prior Authorization Control Number:
A number that uniquely identifies a particular instance of prior authorization.

79. Payment Amount:
The computed amount of payment due a provider for a claim transaction.

80. Date of Adjudication:
The date a claim is approved (or partially approved) or disallowed.

81. Error Code:
A code indicating the nature of an error condition associated with that claim transaction.

82. Date Entered Suspense:
The date a claim transaction was initially suspended.

83. Payment Date:
The date a payment instrument was generated for a claim transaction.

84. Allowable Procedure Payment:
The maximum allowed amount payable for a particular medical procedure, treatment, or service item.

85. Professional Fee:
The amount allowed to a dispenser of drugs as compensation for his professional services.

86. Prescription Number:
The number assigned by a pharmacist to a prescription at the time it is filled.

87. Procedure Codes:
Codes identifying medical procedures (i.e. accept and use exclusively the HCPCS in a physician or outpatient setting). (For an inpatient setting, ICD-9-CM Volume 3 is recommended).

**a. Principal Significant Procedures:
When more than one procedure is reported, designate the principal procedure. In determining which of several procedures is the principal, apply the following criteria:

(1) The principal procedure is the one which was performed for definitive treatment rather than performed for diagnostic or exploratory purposes, or was necessary to take care of a complication.

(2) The principal procedure is that procedure most closely related to the principal diagnosis.

**b. Other Significant Procedures:

(1) One which carries an operative or anesthetic risk, requires highly trained personnel, or requires special facilities or equipment.

(2) Up to four significant procedures can be reported.

(HCFA requires the acceptance of ICD-9-CM coding.)

88. Drug Code:
Codes identifying particular drugs; e.g., National Drug Code, drug tables.

89. Diagnosis Code:
A table of codes identifying medical conditions; i.e., ICD-9-CM.

90. Drug Name:
The generally accepted nomenclature for a particular drug.

91. Drug Classification:
The therapeutic group in to which a drug is categorized.

92. Minimum Days Supply of Drugs:
The minimum units of a drug prescription eligible for payment.

93. Maximum Days Supply of Drug:
The maximum units of a drug prescription eligible for a particular drug.

94. Procedures Names:
The generally accepted nomenclature for medical, surgical, dental, etc., procedure.

95. Diagnosis Name:
The generally accepted nomenclature for a diagnosis. Name is required only if not encoded by provider. (See Data Element No. 6l.)

96. Unit of Measure:
The unit in which a drug is dispensed (e.g., cc, capsule, tablet).

97. Drug Cancellation Date:
The date after which a particular drug is no longer covered under the State Medicaid program.

98. Medicaid Reasonable Charge:
Payment amount recognized as the reasonable charge for Medicaid.

*99. Discharged Patient's Destination:
A code indicating a recipient's destination upon discharge from a medical institution.

a. Discharged to home (routine discharge).
b. Left against medical advice.
c. Discharged to another short term hospital.
d. Discharged to a long term care institution.
e. Died.
f. Other.

100. Billing Date:
The date a provider indicates a claim was prepared.

101. Procedure Charge:
The charge for an individual procedure, treatment, or service item as submitted by the provider.

102. Drug Charge:
The charge submitted by a provider for a given drug prescription.

103. Adjustment Amount:
The amount (plus or minus) by which a provider's account is to be changed.

104. Date Claim Received:
The date on which a claim transaction is received by the claims processing agency.

105. Date of Surgery:
The date on which a surgical procedure(s) was performed on an inpatient.

106. Drug Wholesale Cost:
The generally accepted wholesale cost of a drug.

107. Maximum Allowed Price:
The maximum amount that will be paid for a procedure, treatment, or service item.

108. Valid Sex Indicator:
A code which indicates when a procedure or diagnosis is limited to one sex only.

109. Age Range Indicator:
A code which specifies an age range when a procedure or diagnosis is limited to a particular age group.

110. Budgeted Amount:
The planned expenditures for various Medicaid services over a given period of time.

111. Screening Results Code:
A code indicating the outcome of the various screening tests rendered.

112. Screening Referral Code:
A code indicating the nature of any referrals made as a result of screening.

113. Screening Related Treatment:
A code identifying procedures or services received as a result of screening.

114. Family Planning Code:
A code indicating whether any diagnosis, treatment, drugs, supplies, and devices, counseling service, or other billed services or materials are for the purposes of family planning.

115. Certification Review Indicator:
Indicator showing that review was made of certification of a recipient who has been admitted to institutional care including approval status.

116. Certification/Recertification Date:
The date of certification/recertification of a recipient who has been admitted to institutional care.

117. Certification Status:
An indication of initial certification status of a patient in an institution.

118. Number of Requests for Extension:
The number of times an extension of certification of stay was requested for a patient in an institution.

119. Days Certified Initially:
The number of days stay certified initially for a patient in an institution.

120. Total Days Certified:
The total number of days stay certified for a patient in an institution.

121. Date of Application:
The date that a recipient applied for eligibility status in the Medicaid program.

122. SSN of an Absent Parent:
See 42 CFR 433.138 for the conditions under which this piece of information must be captured.

disorder and other psychiatric disorders. However, FDA also states that depression and certain other psychiatric disorders are themselves associated with an increased risk of suicide. (See Cautions: Pediatric Precautions, in Fluoxetine Hydrochloride 28:16.04.20) Anyone considering the use of mirtazapine in a child or adolescent for any clinical use must therefore balance the potential risks with the clinical need. (See Suicidality Precautions under Dosage and Administration: Dosage.)

■ **Dosage in Renal and Hepatic Impairment** Although clearance of mirtazapine may decrease in patients with hepatic or moderate to severe renal impairment, the manufacturer does not make specific recommendations for dosage adjustment in such patients. However, the manufacturer states that since plasma concentrations of mirtazapine may be increased in patients with hepatic or moderate to severe renal impairment, the drug should be used with caution in such patients.

Description

Mirtazapine is a piperazinoazepine-derivative antidepressant agent. As a tetracyclic antidepressant agent, the drug differs structurally from selective serotonin-reuptake inhibitors (e.g., fluoxetine, sertraline), monoamine oxidase inhibitors, and tricyclic antidepressant agents.

The exact mechanism of antidepressant action of mirtazapine has not been fully elucidated, but the drug appears to act as an antagonist at central presynaptic α_2-adrenergic autoreceptors and heteroreceptors resulting in enhanced central noradrenergic and serotonergic activity. Mirtazapine is a potent antagonist of serotonin type 2 (5-HT_2) and type 3 (5-HT_3) receptors, but the drug does not exhibit high affinity for serotonin type 1A (5-HT_{1A}) or type 1B (5-HT_{1B}) receptors. Mirtazapine is a potent antagonist of histamine H_1 receptors, which may account for the prominent sedative effects of the drug. In addition, the drug exhibits moderate peripheral α_1-adrenergic blocking activity that may explain the occasional orthostatic hypotension that reportedly has been associated with mirtazapine. The drug is a moderate antagonist at muscarinic receptors, which may account for the relatively low incidence of anticholinergic effects associated with mirtazapine.

SumMon® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the labeling be consulted for detailed information on the usual cautions, precautions, and contraindications.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Mirtazapine

Oral		
Tablets, film-coated	15 mg*	**Mirtazapine Film-coated Tablets**
		Remeron* (scored), Organon
	30 mg*	**Mirtazapine Film-coated Tablets**
		Remeron* (scored), Organon
	45 mg*	**Mirtazapine Film-coated Tablets**
		Remeron*, Organon
Tablets, orally disintegrating	15 mg*	**Mirtazapine Orally Disintegrating Tablets**
		Remeron* SolTab, Organon
	30 mg*	**Mirtazapine Orally Disintegrating Tablets**
		Remeron* SolTab, Organon
	45 mg*	**Mirtazapine Orally Disintegrating Tablets**
		Remeron* SolTab, Organon

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

ANTIPSYCHOTICS 28:16.08
ATYPICAL ANTIPSYCHOTICS 28:16.08.04

Aripiprazole

■ Aripiprazole is considered an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Aripiprazole is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Schizophrenia Aripiprazole is used orally for the acute and maintenance treatment of schizophrenia in adults and adolescents 13–17 years of age. Schizophrenia is a major psychotic disorder that frequently has devastating effects on various aspects of the patient's life and carries a high risk of suicide and other life-threatening behaviors. Manifestations of schizophrenia involve multiple psychologic processes, including perception (e.g., hallucinations), ideation, reality testing (e.g., delusions), emotion (e.g., flatness, inappropriate affect), thought processes (e.g., loose associations), behavior (e.g., catatonia, disorganization), attention, concentration, motivation (e.g., avolition, impaired intention and planning), and judgment. The principal manifestations of this disorder usually are described in terms of positive and negative (deficit) symptoms and, more recently, disorganized symptoms. Positive symptoms include hallucinations, delusions, bizarre behavior, hostility, uncooperativeness, and paranoid ideation, while negative symptoms include restricted range and intensity of emotional expression (affective flattening), reduced thought and speech productivity (alogia), anhedonia, apathy, and decreased initiation of goal-directed behavior (avolition). Disorganized symptoms include disorganized speech (thought disorder) and behavior and poor attention.

Short-term efficacy of oral aripiprazole monotherapy in the acute treatment of schizophrenia in adults was evaluated in 5 placebo-controlled studies of 4 and 6 weeks' duration principally in acutely relapsed, hospitalized patients who predominantly met DSM-III/IV criteria for schizophrenia. Four of the 5 studies were able to distinguish aripiprazole from placebo, but the smallest study did not. In the 4 positive studies, assessment of improvement in manifestations of schizophrenia was based on results of psychiatric rating scales, including the Positive and Negative Syndrome Scale (PANSS), the PANSS positive subscale, the PANSS negative subscale, and the Clinical Global Impressions (CGI) scale. Aripiprazole generally was found to be superior to placebo in improving both positive and negative manifestations in acute exacerbations of schizophrenia in these 4 studies. Efficacy of 10-, 15-, 20-, and 30-mg daily dosages of aripiprazole was established in 2 studies for each dosage; however, there was no evidence that higher dosages offered any therapeutic advantage over lower dosages in these studies. Active controls (haloperidol or risperidone) were used in addition to placebo controls in 3 of these studies, but study design did not allow for comparison between aripiprazole and the active controls. An examination of population subgroups did not reveal any clear evidence of differential responsiveness to the drug based on age, gender, or race.

In a longer-term study, adult inpatients or outpatients who met DSM-IV criteria for schizophrenia and who were, by history, symptomatically stable on other antipsychotic agents for at least 3 months were discontinued from those other agents and randomized to receive either oral aripiprazole 15 mg daily or placebo for up to 26 weeks of observation for relapse in the double-blind phase. Relapse was based on results of the CGI-Improvement and PANSS psychiatric rating scales. Patients receiving aripiprazole experienced a significantly longer time to relapse over the subsequent 26 weeks compared with those receiving placebo. In addition, pooled data from 2 double-blind, multicenter studies in acutely ill patients with schizophrenia in whom therapy with aripiprazole or haloperidol was continued for 52 weeks demonstrated a substantially higher rate of symptomatic remission across 52 weeks in the aripiprazole-treated patients compared with the haloperidol-treated patients; improved tolerability with aripiprazole may have contributed to the higher overall remission rates observed in this pooled analysis.

Short-term efficacy of oral aripiprazole in the acute treatment of schizophrenia in adolescents 13–17 years of age was evaluated in a double-blind, placebo-controlled trial of 6 weeks' duration in 302 outpatients who met DSM-IV criteria for schizophrenia and had a PANSS total score of 70 or more at baseline. Patients were randomized to receive a fixed dosage of aripiprazole 10 mg daily or 30 mg daily or to receive placebo. Both dosages of aripiprazole were found to be superior to placebo in reducing the PANSS total score, which was the primary efficacy measure; the 10-mg daily dosage also demonstrated superiority over placebo on the PANSS negative subscale score at the study

end point. However, the 30-mg daily dosage failed to demonstrate superiority over the 10-mg daily dosage. The drug was generally well tolerated.

Although the efficacy of aripiprazole as maintenance therapy in pediatric patients with schizophrenia has not been systematically evaluated, the manufacturer states that such efficacy can be extrapolated from adult data in addition to comparisons of aripiprazole pharmacokinetic parameters in adults and pediatric patients.

If aripiprazole is used for extended periods, the need for continued therapy should be reassessed periodically. (See Dosage and Administration: Dosage and see also Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

The American Psychiatric Association (APA) considers most atypical antipsychotic agents first-line drugs for the management of the acute phase of schizophrenia (including first psychotic episodes), principally because of the decreased risk of adverse extrapyramidal effects and tardive dyskinesia, with the understanding that the relative advantages, disadvantages, and cost-effectiveness of conventional and atypical antipsychotic agents remain controversial. The APA states that, with the possible exception of clozapine for the management of treatment-resistant symptoms, there currently is no definitive evidence that one atypical antipsychotic agent will have superior efficacy compared with another agent in the class, although meaningful differences in response may be observed in individual patients. Conventional antipsychotic agents may be considered first-line therapy in patients who have been treated successfully in the past with or who prefer conventional agents. The choice of an antipsychotic agent should be individualized, considering past response to therapy, adverse effect profile (including the patient's experience of subjective effects such as dysphoria), and the patient's preference for a specific drug, including route of administration.

For additional information on the symptomatic management of schizophrenia, including treatment recommendations and results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, see Schizophrenia and Other Psychotic Disorders under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

■ **Bipolar Disorder** Aripiprazole is used as monotherapy or as an adjunct to either lithium or valproate for the acute and maintenance treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults and pediatric patients 10–17 years of age. According to DSM-IV criteria, manic episodes are distinct periods lasting 1 week or longer (or less than 1 week if hospitalization is required) of abnormally and persistently elevated, expansive, or irritable mood accompanied by at least 3 (or 4 if the mood is only irritability) of the following 7 symptoms: grandiosity, reduced need for sleep, pressure of speech, flight of ideas, distractability, increased goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation, and engaging in high-risk behavior (e.g., unrestrained buying sprees, sexual indiscretions, foolish business investments).

Efficacy of aripiprazole monotherapy in the treatment of acute manic and mixed episodes has been demonstrated in 4 short-term (i.e., 3 weeks' duration), placebo-controlled trials in hospitalized adults who met DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These studies included patients with or without psychotic features and 2 of the studies also included patients with or without a rapid cycling course. The principal rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). The main secondary rating instrument used in these trials was the Clinical Global Impression-Bipolar (CGI-BP) scale. In these trials, aripiprazole 15–30 mg once daily (with an initial dosage of 15 mg daily in 2 studies and an initial dosage of 30 mg daily in the other 2 studies) was found to be superior to placebo in the reduction of the Y-MRS total score and the CGI-BP Severity of Illness score (mania). In the 2 studies with an initial aripiprazole dosage of 15 mg daily, 48 and 44% of patients were receiving 15 mg daily at the study end point; in the 2 studies with an initial dosage of 30 mg daily, 86 and 85% of patients were receiving 30 mg daily at end point.

Aripiprazole is used as monotherapy for the acute and maintenance treatment of manic and mixed episodes associated with bipolar I disorder with or without psychotic features in pediatric patients 10–17 years of age. Efficacy of aripiprazole in the acute treatment of manic and mixed episodes has been demonstrated in a double-blind, placebo-controlled study of 4 weeks' duration in pediatric outpatients who met DSM-IV criteria for bipolar I disorder manic or mixed episodes (with or without psychotic features) and who had Y-MRS scores of 20 or greater at baseline. Patients in this study received aripiprazole 10 mg daily, aripiprazole 30 mg daily, or placebo. Aripiprazole was initiated at a dosage of 2 mg daily, then titrated to 5 mg daily after 2 days, and to the target dosage of 10 mg daily in 5 days or 30 mg daily in 13 days. Both dosages of aripiprazole were found to be superior to placebo in the reduction of the Y-MRS total score from baseline to week 4.

Efficacy of aripiprazole as an adjunct to lithium or valproate in the treatment of acute manic and mixed episodes has been demonstrated in a placebo-controlled study of 6 weeks' duration in adult outpatients who met DSM-IV criteria for bipolar I disorder manic or mixed type (with or without psychotic features). Patients initially received open-label lithium (dosage producing a serum lithium concentration of 0.6–1 mEq/L) or valproate (dosage producing a serum valproic acid concentration of 50–125 mcg/mL) monotherapy for 2 weeks during the lead-in phase. At the end of 2 weeks, patients demonstrating an inadequate response to lithium or valproate were randomized to receive either aripiprazole (15 mg daily or increased to 30 mg daily as early as day 7) or placebo as adjunctive therapy with open-label lithium or valproate during the 6-week, placebo-controlled phase. Patients who received adjunctive aripiprazole with lithium or valproate demonstrated greater reductions in the Y-MRS total score and the CGI-BP Severity of Illness score (mania) compared with patients who received adjunctive placebo with lithium or valproate.

The use of aripiprazole as an adjunct to lithium or valproate in the acute treatment of manic or mixed episodes associated with bipolar I disorder has not been evaluated in the pediatric population. However, the manufacturer states that such efficacy can be extrapolated from adult data in addition to comparisons of aripiprazole pharmacokinetic parameters in adults and pediatric patients.

For the initial management of less severe manic or mixed episodes in patients with bipolar disorder, current APA recommendations state that monotherapy with lithium, valproate (e.g., valproate sodium, valproic acid, divalproex), or an antipsychotic such as olanzapine may be adequate. For more severe manic or mixed episodes, combination therapy with an antipsychotic and lithium or valproate is recommended as first-line therapy. For further information on the management of bipolar disorder, see Uses: Bipolar Disorder, in Lithium Salts 28:28.

The efficacy of aripiprazole as longer-term therapy (i.e., longer than 3 weeks) in adults with bipolar I disorder was demonstrated in a double-blind, placebo-controlled trial in patients with a recent manic or mixed episode who had been stabilized on aripiprazole (15–30 mg daily) and then maintained on the drug for at least 6 consecutive weeks. Following this 6-week maintenance phase, patients were randomized to receive either placebo or aripiprazole and monitored for manic or depressive relapse. Patients receiving aripiprazole experienced a significant delay in time to relapse and there were fewer relapses among those receiving aripiprazole than among those receiving placebo.

An analysis of these data for possible age- and gender-related effects on treatment outcome did not suggest any difference in aripiprazole's efficacy in bipolar disorder based on the age and gender of the patient; however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess race-related effects.

Although the efficacy of aripiprazole as maintenance therapy in pediatric patients with bipolar disorder has not been evaluated, the manufacturer states that such efficacy can be extrapolated from adult data in addition to comparisons of aripiprazole pharmacokinetic parameters in adults and pediatric patients.

The manufacturer states that the efficacy of aripiprazole in bipolar disorder has not been systematically evaluated for long-term use (i.e., exceeding 6 weeks) and recommends that clinicians who elect to use aripiprazole for extended periods periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

■ **Major Depressive Disorder** Aripiprazole is used orally as an adjunct to antidepressants for the acute treatment of major depressive disorder in adults. The adjunctive efficacy of aripiprazole has been demonstrated in 2 short-term, double-blind, placebo-controlled trials of 6 weeks' duration in adults who met DSM-IV criteria for major depressive disorder and who had an inadequate response to previous antidepressant therapy (1–3 courses) in the current episode and who had also demonstrated an inadequate response during a prospective treatment period to 8 weeks of antidepressant therapy with extended-release paroxetine, extended-release venlafaxine, fluoxetine, escitalopram, or sertraline. The primary instrument used for assessing depressive symptoms was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale used to assess the degree of depressive symptomatology. The principal secondary instrument was the Sheehan Disability Scale (SDS), a 3-item self-rated instrument used to assess the impact of depression on three domains of functioning (work/school, social life, and family life), with each item scored from 0 (not at all) to 10 (extreme). In both of these trials, aripiprazole was found to be superior to placebo in reducing mean MADRS total scores; aripiprazole was also superior to placebo in reducing the mean SDS score in one study. Patients in both trials initially received an aripiprazole dosage of 5 mg daily; subsequent dosage adjustments, based on efficacy and tolerability, could be made in 5-mg increments 1 week apart. Allowable aripiprazole dosages were 2, 5, 10, and 15 mg daily; patients who were not receiving the potent cytochrome P-450 (CYP) isoenzyme 2D6 inhibitors fluoxetine and paroxetine could also receive 20 mg daily.

An analysis of population subgroups did not reveal evidence of differential response based on age, choice of prospective antidepressant, or race. With regard to gender, a smaller mean reduction in the MADRS total score was observed in males than in females.

■ **Agitation Associated with Schizophrenia or Bipolar Mania** Aripiprazole is used IM for the acute management of agitation associated with schizophrenia or bipolar disorder, mixed or manic, in adults for whom treatment with aripiprazole is appropriate and who require an IM antipsychotic agent for rapid control of behaviors that interfere with diagnosis and care (e.g., threatening behaviors, escalating or urgently distressing behavior, self-exhausting behavior). According to DSM-IV, psychomotor agitation is defined as excessive motor activity associated with a feeling of inner tension.

The efficacy of IM aripiprazole for the management of acute agitation was established in 3 short-term (i.e., single-day), placebo-controlled trials in hospitalized, agitated patients with either schizophrenia or bipolar I disorder (manic or mixed episodes, with or without psychotic features). Each of the 3

trials used a single active comparator treatment of either haloperidol injection (for the schizophrenia studies) or lorazepam (for the bipolar mania study). Patients enrolled in the studies needed to be judged by the investigators as clinically agitated and appropriate candidates for IM therapy. In addition, the patients needed to exhibit a level of agitation that met or exceeded a threshold score of 15 on the 5 items constituting the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least 2 individual item scores of 4 ("moderate") or greater using a 1–7 scoring system, where scores of 1 or 7 indicate absent or extreme agitation, respectively. The primary measure used for assessing efficacy in managing agitation in these trials was the change from baseline in the PANSS Excited Component at 2 hours postinjection. A key secondary measure was the Clinical Global Impression of Improvement (CGI-I) scale. Patients could receive up to 3 injections of IM aripiprazole; however, patients could not receive the second injection until after the initial 2-hour period when the primary efficacy measure was assessed.

In the first placebo-controlled trial, IM aripiprazole was given in fixed single doses of 1, 5.25, 9.75, or 15 mg in agitated hospitalized patients presenting predominantly with schizophrenia. All IM aripiprazole doses, with the exception of the 1-mg dose, were found to be superior to placebo in reducing the PANSS Excited Component score and on the CGI-I scale at 2 hours following injection in this study. In the second placebo-controlled trial in agitated hospitalized patients predominantly with schizophrenia, one fixed IM dose of aripiprazole 9.75 mg was evaluated and found to be superior to placebo on the PANSS Excited Component and on the CGI-I scale at 2 hours following injection. In the third placebo-controlled trial in agitated hospitalized patients with bipolar I disorder (manic or mixed), 2 fixed aripiprazole injection doses of 9.75 mg and 15 mg were evaluated; both doses were found to be superior to placebo in reducing the PANSS Excited Component score at 2 hours postinjection. An analysis of these 3 controlled studies for possible age-, race-, or gender-related effects on treatment outcome did not suggest any difference in efficacy based on these patient characteristics.

Dosage and Administration

■ **Administration** Aripiprazole conventional tablets, orally disintegrating tablets, and oral solution are administered orally once daily without regard to meals. Aripiprazole injection is administered *only* by IM injection.

Patients receiving aripiprazole orally disintegrating tablets should be instructed not to remove a tablet from the blister package until just prior to dosing. With dry hands, the blister package should be peeled open to expose a tablet. The tablet should then be removed and placed on the tongue, where it rapidly disintegrates in saliva. The manufacturer recommends that the orally disintegrating tablets be taken without liquid; however, they may be taken with liquid, if necessary. Orally disintegrating tablets should *not* be split.

Aripiprazole injection should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The required volume of injection should be withdrawn from the vial into a syringe and then injected slowly IM, deep into the muscle mass. Aripiprazole injection should *not* be administered IV or subcutaneously. Unused portions of the solution should be discarded.

Patients receiving aripiprazole should be monitored for possible worsening of depression, suicidality, or unusual changes in behavior, especially at the beginning of therapy or during periods of dosage adjustment. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

■ **Dosage** Aripiprazole oral solution may be given at the same dose on a mg-per-mg basis as the conventional tablet strengths of the drug up to a dose of 25 mg. However, if the oral solution is used in patients who were receiving aripiprazole 30 mg as conventional tablets, a dose of 25 mg of the oral solution should be used.

Since conventional tablets and orally disintegrating tablets of aripiprazole are bioequivalent, dosing for the orally disintegrating tablets is the same as for the conventional tablets. However, IM administration of a dose of the commercially available injection results in maximum plasma aripiprazole concentrations and areas under the plasma concentration-time curve (AUCs) (2 hours post-administration) that are about 19 and 90% higher, respectively, than those resulting from an identical oral dose.

Schizophrenia For the acute management of schizophrenia in adults, the recommended initial and target dosage of aripiprazole is 10 or 15 mg orally once daily. Although dosages ranging from 10–30 mg daily administered as conventional tablets were effective in clinical trials, the manufacturer states that dosages exceeding 10–15 mg daily did not result in greater efficacy. Because steady-state plasma concentrations of aripiprazole and dehydro-aripiprazole, its active metabolite, may not be attained for 2 weeks, dosage adjustments generally should be made at intervals of not less than 2 weeks.

For the acute management of schizophrenia in adolescents 13–17 years of age, the recommended target dosage of aripiprazole is 10 mg orally once daily. Therapy was initiated in a dosage of 2 mg once daily in these patients, with subsequent titration to 5 mg once daily after 2 days and to 10 mg once daily after 2 additional days. The manufacturer recommends that any subsequent dosage increases be made in 5-mg once daily increments. Although aripiprazole dosages of 10 and 30 mg once daily administered as conventional tablets have been studied in adolescents, the 30-mg daily dosage was not found to be more effective than the 10-mg daily dosage.

The optimum duration of oral aripiprazole therapy in patients with schizophrenia currently is not known, but maintenance therapy with aripiprazole 15 mg once daily as conventional tablets has been shown to be effective in preventing relapse for up to 26 weeks in adults. In addition, a combined analysis of data from 2 double-blind, multicenter studies indicates that maintenance therapy with the drug may be effective for up to 52 weeks in adults.

Although the efficacy of oral aripiprazole as maintenance therapy in pediatric patients with schizophrenia has not been systematically evaluated, the manufacturer states that such efficacy can be extrapolated from adult data in addition to comparisons of aripiprazole pharmacokinetic parameters in adults and pediatric patients.

The American Psychiatric Association (APA) states that prudent long-term treatment options in patients with schizophrenia with remitted first episodes or multiple episodes include either indefinite maintenance therapy or gradual discontinuance of the antipsychotic agent with close follow-up and a plan to reinstitute treatment upon symptom recurrence. Discontinuance of antipsychotic therapy should be considered only after a period of at least 1 year of symptom remission or optimal response while receiving the antipsychotic agent. In patients who have had multiple previous psychotic episodes or 2 psychotic episodes within 5 years, indefinite maintenance antipsychotic treatment is recommended.

The manufacturer states that it is generally recommended that patients responding to aripiprazole therapy should continue to receive the drug beyond the acute response, but at the lowest dosage needed to maintain remission. The need for continued therapy with the drug should be reassessed periodically.

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotic agents to aripiprazole or concerning concomitant administration with other antipsychotic agents. Immediate discontinuance of the previous antipsychotic agent may be acceptable in some patients with schizophrenia, and more gradual discontinuance may be most appropriate for other patients. In all patients, the period of overlapping antipsychotic administration should be minimized.

Bipolar Disorder For the management of manic and mixed episodes associated with bipolar I disorder in adults, the recommended initial and target aripiprazole dosage in adults is 15 mg given orally once daily as monotherapy or as adjunctive therapy with lithium or valproate. Based on clinical response, the dosage can be increased to 30 mg daily. However, safety of aripiprazole dosages exceeding 30 mg daily has not been established.

For the management of manic and mixed episodes associated with bipolar I disorder in pediatric patients 10–17 years of age, the manufacturer recommends a target aripiprazole dosage of 10 mg daily given orally as monotherapy or as adjunctive therapy with lithium or valproate. In clinical studies, aripiprazole dosages of 10 or 30 mg daily were found to be effective; initially, pediatric patients received 2 mg daily for 2 days, then 5 mg daily for an additional 2 days, and then the target dosage of 10 mg daily. Subsequent increases in the daily dosage of aripiprazole should be made in 5-mg increments.

The optimum duration of aripiprazole therapy, whether used as monotherapy or as adjunctive therapy, for bipolar I disorder currently is not known. While it is generally agreed that pharmacologic treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of aripiprazole beyond 6 weeks in adults. The manufacturer states that clinicians who elect to use aripiprazole in adults for extended periods should periodically reevaluate the long-term risks and benefits of the drug for the individual patient.

The efficacy of aripiprazole for maintenance therapy of bipolar I disorder in pediatric patients has not been evaluated; however, such efficacy can be extrapolated from adult data along with comparisons of pharmacokinetic parameters of the drug in adults and pediatric patients. It is generally recommended that responding pediatric patients continue to receive aripiprazole beyond the acute response, but at the lowest dosage needed to maintain remission. Pediatric patients should be periodically reassessed to determine the need for maintenance therapy.

Major Depressive Disorder For adjunctive management of major depressive disorder in adults already receiving an antidepressant, the manufacturer recommends an initial aripiprazole dosage of 2–5 mg orally once daily for acute treatment. Subsequent dosage adjustments of up to 5 mg daily should occur gradually at intervals of at least 1 week. Efficacy of the drug was established within a dosage range of 2–15 mg daily in clinical studies.

The manufacturer states that the efficacy of aripiprazole for adjunctive maintenance treatment of major depressive disorder has not been evaluated and the optimum duration of aripiprazole maintenance therapy for major depressive disorder is not known. If aripiprazole is used for maintenance therapy, the need for continued therapy with the drug should be reassessed periodically.

Agitation associated with Schizophrenia or Bipolar Mania For the prompt control of agitation associated with schizophrenia or bipolar mania in adults, the recommended dose of aripiprazole is 9.75 mg given IM as a single dose. In clinical trials, effectiveness of IM aripiprazole in controlling agitation in schizophrenia and bipolar mania was demonstrated with doses of 5.25–15 mg IM; however, no additional benefit was demonstrated for the 15-mg dose compared with the 9.75-mg dose. A lower initial IM dose of 5.25 mg may be considered when clinically warranted.

If agitation persists following the initial dose of aripiprazole, subsequent doses up to a cumulative dose of 30 mg daily may be given. However, the

manufacturer states that the efficacy of repeated doses of IM aripiprazole in agitated patients has not been systematically evaluated in controlled trials. In addition, the safety of total daily IM doses exceeding 30 mg or IM injections given more frequently than every 2 hours has not been adequately evaluated in clinical trials.

If continued aripiprazole therapy is clinically necessary, oral aripiprazole therapy in a dosage of 10–30 mg daily should replace IM therapy as soon as possible.

■ **Special Populations** No dosage adjustment is necessary in patients with renal or hepatic impairment or in geriatric patients. In addition, no dosage adjustment is recommended based on gender or race.

Dosage of aripiprazole should be reduced to one-half the usual dosage in patients receiving concomitant therapy with potent inhibitors of cytochrome P-450 (CYP) isoenzyme 3A4 (e.g., clarithromycin, ketoconazole). Dosage of aripiprazole should be reduced to at least one-half the usual dosage in patients receiving concomitant therapy with potential inhibitors of CYP2D6 (e.g., quinidine, fluoxetine, paroxetine). The aripiprazole dosage may be increased to the usual dosage after discontinuance of the CYP3A4 or CYP2D6 inhibitor. (See Drug Interactions: Ketoconazole and Other CYP3A4 Inhibitors and see also Drug Interactions: Quinidine and Other CYP2D6 Inhibitors.)

Dosage of aripiprazole should be doubled upon initiation of concomitant therapy with drugs that induce CYP3A4 (e.g., carbamazepine); additional dosage escalation should be based on clinical evaluation. The aripiprazole dosage should be decreased to 10–15 mg daily if the CYP3A4 inducer is discontinued. (See Drug Interactions: Carbamazepine and Other CYP3A4 Inducers.)

Cautions

■ **Contraindications** Known hypersensitivity reaction to aripiprazole or any ingredient in the formulation; such reactions have ranged from pruritus/urticaria to anaphylaxis.

■ **Warnings/Precautions** ***Warnings*** **Increased Mortality in Geriatric Patients with Dementia-related Psychosis.** Geriatric patients with dementia-related psychosis treated with antipsychotic drugs appear to be at an increased risk of death compared with patients receiving placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) revealed an approximate 1.6- to 1.7-fold increase in mortality among geriatric patients receiving atypical antipsychotic drugs (i.e., aripiprazole, olanzapine, quetiapine, risperidone) compared with that observed in patients receiving placebo. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared with a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotics, treatment with conventional (first-generation) antipsychotics may increase mortality; the extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients remains unclear. In addition, an increased incidence of cerebrovascular adverse effects (e.g., stroke, transient ischemic attack), including fatalities, has been observed in geriatric patients treated with aripiprazole in several placebo-controlled studies (2 flexible-dose studies and one fixed-dose study) of dementia-related psychosis. A statistically significant dose-response relationship for adverse cerebrovascular effects was observed in patients receiving the drug in the fixed-dose study. In 3 placebo-controlled trials of 10 weeks' duration evaluating aripiprazole in geriatric patients with psychosis associated with Alzheimer's disease, adverse effects reported in 3% or more of patients and with an incidence of at least twice that of placebo included lethargy, somnolence (including sedation), incontinence (primarily urinary incontinence), excessive salivation, and lightheadedness.

The manufacturer states that the safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with dementia have not been established and that the drug is not approved for the treatment of patients with dementia-related psychosis. If the clinician elects to treat such patients with aripiprazole, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration. (See Geriatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Worsening of Depression and Suicidality Risk. Worsening of depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior may occur in both adult and pediatric (see Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions) patients with major depressive disorder or other psychiatric disorders, whether or not they are taking antidepressants. This risk may persist until clinically important remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. However, there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled studies of antidepressants (i.e., selective serotonin-reuptake inhibitors and other antidepressants) have shown an increased risk of suicidality in children, adolescents, and young adults (18–24 years of age) with major depressive disorder and other psychiatric disorders. An increased suicidality risk was not demonstrated with antidepressants compared with placebo in adults older than 24 years of age and a reduced risk was observed in adults 65 years of age or older.

The US Food and Drug Administration (FDA) recommends that all patients being treated with antidepressants for any indication be appropriately monitored and closely observed for clinical worsening, suicidality, and unusual changes in behavior, particularly during initiation of therapy (i.e., the first few months) and during periods of dosage adjustments. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, also should be advised to monitor patients on a daily basis for the emergence of agitation, irritability, or unusual changes in behavior as well as the emergence of suicidality, and to report such symptoms immediately to a health-care provider.

Although a causal relationship between the emergence of symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and/or mania and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consequently, consideration should be given to changing the therapeutic regimen or discontinuing therapy in patients whose depression is persistently worse or in patients experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, particularly if such manifestations are severe, abrupt in onset, or were not part of the patient's presenting symptoms. FDA also recommends that the drugs be prescribed in the smallest quantity consistent with good patient management, in order to reduce the risk of overdosage.

It is generally believed (though not established in controlled trials) that treating a major depressive episode with an antidepressant alone may increase the likelihood of precipitating a mixed or manic episode in patients at risk for bipolar disorder. Therefore, patients with depressive symptoms should be adequately screened for bipolar disorder prior to initiating treatment with an antidepressant; such screening should include a detailed psychiatric history (e.g., family history of suicide, bipolar disorder, and depression).

Aripiprazole is not approved for use in treating depression in the pediatric population. (See Pediatric Use under Warnings/Precautions: Specific Populations, in Cautions.)

Other Warnings and Precautions **Neuroleptic Malignant Syndrome.** Neuroleptic malignant syndrome (NMS), a potentially fatal syndrome requiring immediate discontinuance of the drug and intensive symptomatic treatment, has been reported in patients receiving antipsychotic agents, including rare cases associated with aripiprazole therapy. If a patient requires antipsychotic therapy following recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If antipsychotic therapy is reintroduced, the dosage generally should be increased gradually and an antipsychotic agent other than the agent believed to have precipitated NMS generally should be chosen. In addition, such patients should be carefully monitored since recurrences of NMS have been reported in some patients. For additional information on NMS, see Neuroleptic Malignant Syndrome under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Tardive Dyskinesia. Because use of antipsychotic agents, including aripiprazole, may be associated with tardive dyskinesia (a syndrome of potentially irreversible, involuntary, dyskinetic movements), aripiprazole should be prescribed in a manner that is most likely to minimize the occurrence of this syndrome. Chronic antipsychotic treatment generally should be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic agents, and for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the lowest dosage and the shortest duration of treatment producing a satisfactory clinical response should be sought, and the need for continued treatment should be reassessed periodically. The American Psychiatric Association (APA) currently recommends that patients receiving atypical antipsychotic agents be assessed clinically for abnormal involuntary movements every 12 months and that patients considered to be at increased risk for tardive dyskinesia be assessed every 6 months. For additional information on tardive dyskinesia, see Tardive Dyskinesia under Cautions: Nervous System Effects, in the Phenothiazines General Statement 28:16.08.24.

Hyperglycemia and Diabetes Mellitus. Severe hyperglycemia, sometimes associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with all atypical antipsychotic agents. While confounding factors such as an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population make it difficult to establish with certainty the relationship between use of agents in this drug class and glucose abnormalities, epidemiologic studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotic agents included in the studies (e.g., clozapine, olanzapine, quetiapine, risperidone); it remains to be determined whether aripiprazole also is associated with this increased risk. Although there have been few reports of hyperglycemia in patients receiving aripiprazole, it is not known whether the paucity of such reports is due to relatively limited experience with the drug.

Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics currently are not available. While some evidence suggests that the risk for diabetes may be greater with some atypical antipsychotics (e.g., clozapine, olanzapine) than with others (e.g., quetiapine, risperidone) in the class, available data are conflicting and insufficient to provide reliable estimates of relative risk associated with use of the various atypical antipsychotics.

The manufacturers of atypical antipsychotic agents state that patients with preexisting diabetes mellitus in whom therapy with an atypical antipsychotic is initiated should be closely monitored for worsening of glucose control; those with risk factors for diabetes (e.g., obesity, family history of diabetes) should undergo fasting blood glucose testing upon therapy initiation and periodically throughout treatment. Any patient who develops manifestations of hyperglycemia (including polydipsia, polyuria, polyphagia, and weakness) during treatment with an atypical antipsychotic should undergo fasting blood glucose testing. In some cases, patients who developed hyperglycemia while receiving an atypical antipsychotic have required continuance of antidiabetic treatment despite discontinuance of the suspect drug; in other cases, hyperglycemia resolved with discontinuance of the antipsychotic.

For further information on managing the risk of hyperglycemia and diabetes mellitus associated with atypical antipsychotic agents, see Hyperglycemia and Diabetes Mellitus under Cautions: Precautions and Contraindications, in Clozapine 28:16.08.04.

Orthostatic Hypotension. Orthostatic hypotension and associated adverse effects (e.g., postural dizziness, syncope) have been reported in patients receiving oral or IM aripiprazole. The drug should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, and/or conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy).

If parenteral benzodiazepine therapy is necessary in patients receiving IM aripiprazole, patients should be monitored for excessive sedation and orthostatic hypotension. (See Drug Interactions: Lorazepam and Other Benzodiazepines.)

Leukopenia, Neutropenia, and Agranulocytosis. In clinical trial and/or postmarketing experience, leukopenia and neutropenia have been temporally related to antipsychotic agents, including aripiprazole. Agranulocytosis also has been reported.

Risk factors for leukopenia and neutropenia include preexisting low leukocyte count and a history of drug-induced leukopenia and neutropenia. Patients with a history of clinically important low leukocyte count or drug-induced leukopenia and neutropenia should have their complete blood count monitored frequently during the first few months of therapy. Discontinuance of aripiprazole should be considered at the first sign of a clinically important decline in leukocyte count in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other signs or symptoms of infection and promptly treated if such signs and symptoms occur. In patients with severe neutropenia (absolute neutrophil count [ANC] less than 1000/mm^3), aripiprazole should be discontinued and the leukocyte count monitored until recovery occurs. Lithium has reportedly been used successfully in the treatment of several cases of leukopenia associated with aripiprazole, clozapine, and some other drugs; however, further clinical experience is needed to confirm these anecdotal findings.

Seizures. Seizures have occurred in 0.1% of adults treated with oral aripiprazole, in 0.3% of pediatric patients 10–17 years of age, and in 0.2% of adults treated with parenteral aripiprazole. Aripiprazole should be used with caution in patients with a history of seizures or other conditions that may lower the seizure threshold (e.g., dementia of the Alzheimer's type); conditions that lower the seizure threshold may be more prevalent in geriatric patients 65 years of age or older.

Cognitive and Motor Impairment. Like other antipsychotic agents, aripiprazole potentially may impair judgment, thinking, or motor skills. In short-term clinical trials, somnolence (including sedation) was reported in 11 and 9% of adults treated with oral or parenteral aripiprazole, respectively, compared with 6% of those receiving placebo. In pediatric patients 10–17 years of age, somnolence (including sedation) was reported in 21% of aripiprazole-treated patients compared with 5% of those receiving placebo. (See Advice to Patients.)

Body Temperature Regulation. Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. The manufacturer recommends appropriate caution when aripiprazole is used in patients exposed to conditions that may contribute to an elevation in core body temperature (e.g., dehydration, extreme heat, strenuous exercise, concomitant use of anticholinergic agents).

Suicide. Attendant risk with psychotic illnesses, bipolar disorder, and major depressive disorder; high-risk patients should be closely supervised. In 2 clinical trials evaluating aripiprazole as adjunctive therapy in patients with major depressive disorder, there were no reported cases of suicidal ideation or suicide attempt in the aripiprazole-treated patients; the incidence of suicidal ideation and suicide attempt was 0.5% in the placebo recipients. Aripiprazole should be prescribed in the smallest quantity consistent with good patient management to reduce the risk of overdosage. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Dysphagia. Esophageal dysmotility and aspiration have been associated with the use of antipsychotic agents, including aripiprazole. These agents should be used with caution in patients at risk for aspiration pneumonia (e.g., geriatric patients, those with advanced Alzheimer's dementia). (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions and see Geriatric Use under Warnings/Precautions: Special Populations, in Cautions.)

Phenylketonuria. Individuals with phenylketonuria (i.e., homozygous genetic deficiency of phenylalanine hydroxylase) and other individuals who must restrict their intake of phenylalanine should be warned that each aripiprazole 10- or 15-mg orally disintegrating tablet contains aspartame, which is metabolized in the GI tract to provide about 1.12 or 1.68 mg of phenylalanine, respectively, following oral administration. Aripiprazole conventional tablets do not contain aspartame.

Concomitant Illnesses. Experience with aripiprazole in patients with certain concomitant diseases is limited. (See Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions.)

Aripiprazole has not been adequately evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable cardiovascular disease and patients with these conditions were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension associated with aripiprazole, the manufacturer states that the drug should be used with caution in patients with cardiovascular disease, cerebrovascular disease, and/or other conditions that would predispose patients to hypotension (e.g., dehydration, hypovolemia, concomitant antihypertensive therapy). (See Orthostatic Hypotension under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

Specific Populations **Pregnancy.** Category C. (See Users Guide.)

Lactation. Aripiprazole is distributed into milk in rats. Not known whether aripiprazole is distributed into milk in humans. The manufacturer states that women receiving aripiprazole should not breast-feed.

Pediatric Use. Safety and efficacy of oral aripiprazole not established in pediatric patients with major depressive disorder. Safety and efficacy of IM aripiprazole not established for agitation associated with schizophrenia or bipolar mania in pediatric patients.

Safety and efficacy of oral aripiprazole for the acute management of schizophrenia in pediatric patients 13–17 years of age have been established in a placebo-controlled study of 6 weeks' duration. Although the efficacy of oral aripiprazole for maintenance treatment of schizophrenia has not been systematically evaluated, the manufacturer states that such efficacy can be extrapolated from adult data in addition to comparisons of aripiprazole pharmacokinetic parameters in adults and pediatric patients. (See Schizophrenia under Uses: Psychotic Disorders.)

Safety and efficacy of oral aripiprazole monotherapy for the acute management of bipolar mania in pediatric patients 10–17 years of age have been established in a placebo-controlled study of 4 weeks' duration. Although the efficacy of oral aripiprazole for maintenance treatment in bipolar disorder has not been established, such efficacy can be extrapolated from adult data in addition to pharmacokinetic comparisons of aripiprazole between adult and pediatric populations.

The efficacy of oral aripiprazole as an adjunct to lithium or valproate for the management of manic or mixed episodes in pediatric patients has not been evaluated. However, efficacy can be extrapolated from adult data in addition to pharmacokinetic comparisons of aripiprazole between adult and pediatric populations.

Mean weight gain of 0.13 kg was reported in pediatric patients with schizophrenia receiving aripiprazole compared with a mean loss of 0.83 kg in those receiving placebo in a short-term (6-week) study; 5% of aripiprazole-treated patients gained 7% or more of their baseline weight compared with 1% of those receiving placebo.

FDA warns that a greater risk of suicidal thinking or behavior (suicidality) occurred during the first few months of antidepressant treatment compared with placebo in children and adolescents with major depressive disorder, obsessive-compulsive disorder (OCD), or other psychiatric disorders based on pooled analyses of 24 short-term, placebo-controlled trials of 9 antidepressant drugs (selective serotonin-reuptake inhibitors [SSRIs] and other antidepressants). However, a more recent meta-analysis of 27 placebo-controlled trials of 9 antidepressants (SSRIs and others) in patients younger than 19 years of age with major depressive disorder, OCD, or non-OCD anxiety disorders suggests that the benefits of antidepressant therapy in treating these conditions may outweigh the risks of suicidal behavior or suicidal ideation. No suicides occurred in these pediatric trials.

These findings should be carefully considered when assessing potential benefits and risks of aripiprazole in a child or adolescent for any clinical use. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

Geriatric Use. In clinical studies, approximately 8% of over 13,000 patients treated with oral aripiprazole were 65 years of age or older and approximately 6% were 75 years of age or older; the majority of these geriatric patients (81%) were diagnosed with dementia of the Alzheimer's type. Experience from placebo-controlled trials with oral aripiprazole in patients with schizophrenia, bipolar mania, or major depressive disorder who are 65 years of age and older is insufficient to determine whether they respond differently than younger adults.

In clinical studies, approximately 13% of over 700 patients treated with IM aripiprazole were 65 years of age or older and approximately 10% were 75 years of age or older. Experience from placebo-controlled trials with aripiprazole injection in patients with agitation associated with schizophrenia or bipolar mania who are 65 years of age and older is insufficient to determine whether they respond differently than younger adults.

Studies in patients with psychosis in association with dementia of the Alz-

heimer's type have suggested that aripiprazole may have a different tolerability profile in patients 65 years of age or older compared with younger patients with schizophrenia. The manufacturer states that the safety and efficacy of aripiprazole in the treatment of dementia-associated psychosis have not been established and that the drug is *not* approved for the treatment of dementia-related psychosis. If a clinician decides to treat geriatric patients with dementia-associated psychosis with aripiprazole, the manufacturer recommends that caution be exercised (see Increased Mortality in Geriatric Patients with Dementia-related Psychosis under Warnings/Precautions: Warnings, in Cautions). For additional information on the use of antipsychotic agents in the management of dementia-related psychosis, see Geriatric Considerations under Uses: Psychotic Disorders, in the Phenothiazines General Statement 28:16.08.24.

In pooled data analyses, a *reduced* risk of suicidality was observed in adults 65 years of age or older with antidepressant therapy compared with placebo. (See Worsening of Depression and Suicidality Risk under Warnings/Precautions: Warnings, in Cautions.)

■ **Common Adverse Effects** Adverse effects occurring in 10% or more of adults receiving oral aripiprazole in clinical trials include nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness.

Adverse effects occurring in 10% or more of pediatric patients receiving oral aripiprazole in clinical trials include somnolence, extrapyramidal disorder, headache, and nausea.

In clinical trials, nausea was the only adverse effect that occurred in more than 5% of patients with agitation associated with schizophrenia or bipolar mania receiving IM aripiprazole and at an incidence at least twice that for placebo.

Drug Interactions

■ **Drugs Affecting Hepatic Microsomal Enzymes** Cytochrome P-450 (CYP) isoenzyme 3A4 (CYP3A4) inducers (e.g., carbamazepine), CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole), or CYP2D6 inhibitors (e.g., fluoxetine, paroxetine, quinidine): potential pharmacokinetic interaction (altered aripiprazole metabolism); dosage adjustment generally recommended. (See Dosage and Administration: Special Populations, Drug Interactions: Carbamazepine and Other CYP3A4 Inducers, Drug Interactions: Ketoconazole and Other CYP3A4 Inhibitors, and Drug Interactions: Quinidine and Other CYP2D6 Inhibitors.)

Inhibitors or inducers of CYP isoenzyme 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, or 2E1: pharmacokinetic interaction unlikely. (See Drug Interactions: Smoking.)

■ **Drugs Metabolized by Hepatic Microsomal Enzymes** Substrates of CYP isoenzyme 1A2, 2C9, 2C19, 2D6, and 3A4: pharmacokinetic interaction unlikely.

■ **Carbamazepine and Other CYP3A4 Inducers** Concurrent administration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, and aripiprazole (30 mg daily) resulted in an approximate 70% decrease in peak plasma concentration and area under the plasma concentration-time curve (AUC) values of both aripiprazole and its active metabolite, dehydro-aripiprazole.

When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the dosage of aripiprazole should be doubled; additional dosage increases should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from combined therapy, the aripiprazole dosage should be reduced to 10–15 mg daily. (See Dosage and Administration: Special Populations.)

■ **Ketoconazole and Other CYP3A4 Inhibitors** Concurrent administration of ketoconazole (200 mg daily for 14 days), a potent CYP3A4 inhibitor, and a single 15-mg dose of aripiprazole increased the AUCs of aripiprazole and its active metabolite by 63 and 77%, respectively; the effect of a higher ketoconazole dosage (e.g., 400 mg daily) has not been studied.

When concurrent therapy with aripiprazole and a potent CYP3A4 inhibitor such as ketoconazole or clarithromycin is clinically indicated, the dosage of aripiprazole should be reduced to one-half of the usual dosage. Other potent inhibitors of CYP3A4 (e.g., itraconazole) would be expected to have similar effects and require similar dosage reductions; the effect of moderate inhibitors (e.g., erythromycin, grapefruit juice) has not been studied. When the CYP3A4 inhibitor is withdrawn from combined therapy, the aripiprazole dosage should be increased. (See Dosage and Administration: Special Populations.)

■ **Quinidine and Other CYP2D6 Inhibitors** Concomitant administration of a single 10-mg dose of aripiprazole with quinidine (166 mg daily for 13 days), a potent CYP2D6 inhibitor, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Other drugs that substantially inhibit CYP2D6 (e.g., fluoxetine, paroxetine) would be expected to have similar effects as quinidine.

When aripiprazole is given concurrently with potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine, the dosage of aripiprazole should be reduced to at least one-half of the usual dosage. When the CYP2D6 inhibitor is withdrawn from combined therapy, the aripiprazole dosage should then be increased. When adjunctive aripiprazole is administered to patients with major depressive disorder, aripiprazole should be given without dosage adjustment. (See Major Depressive Disorder under Dosage and Administration: Dosage, and see also Drug Interactions: Fluoxetine, Paroxetine, and Sertraline.)

■ **Anticholinergic Agents** Potential pharmacologic interaction (possible disruption of body temperature regulation); use aripiprazole with caution in patients concurrently receiving drugs with anticholinergic activity. (See Body Temperature Regulation under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Hypotensive Agents** Potential pharmacologic interaction (additive hypotensive effects); use with caution.

■ **Lorazepam and Other Benzodiazepines** Clinically important pharmacokinetic changes not reported during concurrent administration of parenteral lorazepam and IM aripiprazole. The manufacturer states that aripiprazole dosage adjustment is not necessary when aripiprazole is concurrently administered with lorazepam. However, increased sedative and orthostatic hypotensive effects have been reported in patients receiving these drugs in combination. If therapy with IM aripiprazole in conjunction with a parenteral benzodiazepine is considered necessary, the patient should be carefully monitored for excessive sedation and orthostatic hypotension. (See Orthostatic Hypotension and see also Cognitive and Motor Impairment under Warnings/Precautions: Other Warnings and Precautions, in Cautions.)

■ **Other CNS Agents or Alcohol** Potential pharmacologic interaction (additive CNS effects). Use with caution.

■ **Dextromethorphan** Clinically important pharmacokinetic interaction unlikely. Dosage adjustment of dextromethorphan is not necessary when administered concomitantly with aripiprazole.

■ **Famotidine** Potential pharmacokinetic interaction (decreased aripiprazole rate and extent of absorption); not clinically important and no dosage adjustment of aripiprazole is necessary when administered concurrently with famotidine.

■ **Lamotrigine** Combined aripiprazole and lamotrigine therapy appears to be well tolerated in patients with bipolar disorder. Pharmacokinetic interaction unlikely; no dosage adjustment of lamotrigine is necessary when aripiprazole is administered concurrently.

■ **Lithium** Clinically important pharmacokinetic interaction unlikely; no dosage adjustment of aripiprazole or lithium is necessary during concurrent administration.

■ **Omeprazole** Concurrent administration of aripiprazole 10 mg daily for 15 days in healthy individuals did not substantially alter the pharmacokinetics of a single 20-mg dose of omeprazole, a CYP2C19 substrate. Dosage adjustment of omeprazole is not necessary when administered concurrently with aripiprazole.

■ **Escitalopram** Concurrent administration of aripiprazole 10 mg daily for 14 days in healthy individuals did not substantially alter the steady-state pharmacokinetics of 10 mg daily of escitalopram, a CYP2C19 and CYP3A4 substrate. Dosage adjustment of escitalopram is not necessary when aripiprazole is added to escitalopram therapy.

■ **Fluoxetine, Paroxetine, and Sertraline** A population pharmacokinetic analysis in patients with major depressive disorder did not demonstrate substantial changes in the pharmacokinetics of fluoxetine, paroxetine, or sertraline (dosed to steady state) following the addition of aripiprazole therapy.

However, fluoxetine and paroxetine are inhibitors of CYP2D6 and the manufacturer recommends that aripiprazole dosage be reduced to one-half the usual dosage in patients receiving concomitant therapy with inhibitors of CYP2D6, including fluoxetine and paroxetine. When the CYP2D6 inhibitor is withdrawn from combined therapy with aripiprazole, the aripiprazole dosage should be increased. When adjunctive aripiprazole is concurrently administered to patients with major depressive disorder receiving fluoxetine or paroxetine, aripiprazole should be given without dosage adjustment. (See Dosage and Administration: Special Populations and see also Drug Interactions: Quinidine and Other CYP2D6 Inhibitors.)

■ **Smoking** Pharmacokinetic interaction unlikely. Dosage adjustment in patients who smoke is not necessary.

■ **Valproate** Clinically important pharmacokinetic interaction unlikely; no dosage adjustment of aripiprazole or valproate is necessary during concurrent administration.

■ **Venlafaxine** Concurrent administration of aripiprazole 10–20 mg daily for 14 days in healthy individuals did not substantially alter the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg daily of extended-release venlafaxine, a CYP2D6 substrate. Dosage adjustment of venlafaxine is not necessary when aripiprazole is added to venlafaxine therapy.

■ **Warfarin** Concurrent administration of aripiprazole 10 mg daily for 14 days did not substantially affect warfarin pharmacokinetics or the international normalized ratio (INR), suggesting a lack of a clinically important effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. Warfarin dosage adjustment is not necessary when administered concurrently with aripiprazole.

Description

Aripiprazole is a quinolinone derivative antipsychotic agent that differs chemically from other currently available antipsychotic agents (e.g., butyro-

phenones, phenothiazines) and has been referred to as an atypical or second-generation antipsychotic agent. The exact mechanism of action of aripiprazole in schizophrenia, bipolar mania, major depressive disorder, and agitation associated with schizophrenia or bipolar mania has not been fully elucidated but, like that of other drugs with efficacy in these conditions (e.g., olanzapine, risperidone, ziprasidone), may involve the drug's activity at dopamine D_2 and serotonin type 1 ($5\text{-}HT_{1A}$) and type 2 ($5\text{-}HT_{2A}$) receptors. However, aripiprazole appears to differ from other atypical antipsychotic agents because the drug demonstrates partial agonist activity at D_2 and $5\text{-}HT_{1A}$ receptors and antagonist activity at $5\text{-}HT_{2A}$ receptors. Antagonism at other receptors (e.g., α_1-adrenergic receptors, histamine H_1 receptors) may contribute to other therapeutic and adverse effects (e.g., orthostatic hypotension, somnolence) observed with aripiprazole.

Aripiprazole is extensively metabolized in the liver principally via dehydrogenation, hydroxylation, and *N*-dealkylation by the cytochrome P-450 (CYP) 2D6 and 3A4 isoenzymes. The major active metabolite of aripiprazole, dehydro-aripiprazole, exhibits affinity for D_2 receptors similar to that of the parent compound and represents approximately 40% of aripiprazole area under the concentration-time curve (AUC) in plasma. Steady-state plasma concentrations of both aripiprazole and dehydro-aripiprazole are achieved within 14 days. The elimination half-lives of aripiprazole and dehydro-aripiprazole are approximately 75 and 94 hours, respectively. Approximately 18% and less than 1% of aripiprazole is excreted unchanged in feces and urine, respectively.

Advice to Patients

Importance of providing copy of written patient information (medication guide) each time aripiprazole is dispensed. Importance of advising patients to read the patient information before taking aripiprazole and each time the prescription is refilled.

Increased mortality in geriatric patients with dementia-related psychosis; importance of advising patients and caregivers that geriatric patients with dementia-related psychosis treated with antipsychotic agents are at an increased risk of death. Patients and caregivers should also be informed that aripiprazole is *not* approved for treating geriatric patients with dementia-related psychosis.

Risk of suicidality; importance of patients, family, and caregivers being alert to and immediately reporting emergence of suicidality, worsening depression, or unusual changes in behavior, especially during the first few months of therapy or during periods of dosage adjustment.

Because somnolence and impairment of judgment, thinking, or motor skills may be associated with aripiprazole, avoid driving, operating machinery, or performing hazardous tasks while taking aripiprazole until the drug's effects on the individual are known. Importance of avoiding alcohol during aripiprazole therapy.

Risk of neuroleptic malignant syndrome (NMS), a rare but life-threatening syndrome that can cause high fever, stiff muscles, sweating, fast or irregular heart beat, change in blood pressure, confusion, and kidney damage. Importance of informing patients to immediately contact a healthcare professional if such symptoms develop.

Importance of clinicians informing patients in whom chronic aripiprazole use is contemplated of risk of tardive dyskinesia. Importance of informing patients to report any muscle movements that cannot be stopped to a healthcare professional.

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs, as well as any concomitant illnesses (e.g., diabetes mellitus).

Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed.

Importance of avoiding overheating or dehydration.

For patients taking aripiprazole orally disintegrating tablets, importance of not removing a tablet from the blister package until just before administering a dose; importance of peeling blister open with dry hands and placing tablet on tongue to dissolve and be swallowed with saliva.

Importance of informing patients with phenylketonuria that aripiprazole orally disintegrating 10- and 15-mg tablets contain 1.12 and 1.68 mg of phenylalanine, respectively.

Importance of being aware that aripiprazole oral solution contains 400 mg of sucrose and 200 mg of fructose per mL.

Importance of informing patients of other important precautionary information. (See Cautions.)

Overview* (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. It is *essential* that the manufacturer's labeling be consulted for more detailed information on usual cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Aripiprazole

Oral		
Solution	5 mg/5 mL	**Abilify* Oral Solution**, Otsuka (also promoted by Bristol-Myers Squibb)
Tablets	2 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
	5 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
	10 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
	15 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
	20 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
	30 mg	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)
Tablets, orally disintegrating	10 mg	**Abilify* Discmelt***, Otsuka (also promoted by Bristol-Myers Squibb)
	15 mg	**Abilify* Discmelt***, Otsuka (also promoted by Bristol-Myers Squibb)
Parenteral		
Injection, for IM use only	7.5 mg/mL (9.75 mg)	**Abilify***, Otsuka (also promoted by Bristol-Myers Squibb)

Clozapine

■ Clozapine has been referred to as an atypical or second-generation antipsychotic agent.

Uses

■ **Psychotic Disorders** Clozapine is used for the symptomatic management of psychotic disorders (e.g., schizophrenia). Drug therapy is integral to the management of acute psychotic episodes and accompanying violent behavior in patients with schizophrenia and generally is required for long-term stabilization to sustain symptom remission or control and to minimize the risk of relapse. Antipsychotic agents are the principal class of drugs used for the management of all phases of schizophrenia and generally are effective in all subtypes of the disorder and subgroups of patients. Patient response and tolerance to antipsychotic agents are variable, and patients who do not respond to or tolerate one drug may be successfully treated with an agent from a different class or with a different adverse effect profile.

Clozapine has been shown to be an effective, relatively rapid-acting, broad-spectrum antipsychotic agent in both uncontrolled and controlled studies of patients with schizophrenia. In these studies, improvement in manifestations of schizophrenia was based on the results of various psychiatric rating scales, principally the Brief Psychiatric Rating Scale (BPRS) that assesses factors such as anergy, thought disturbance, activation, hostility/suspiciousness, and anxiety/depression. In clinical studies, clozapine improved both positive (florid symptomatology such as hallucinations, conceptual disorganization, and suspiciousness) and negative ("deficit" symptomatology such as emotional withdrawal, motor retardation, blunted affect, and disorientation) manifestations of schizophrenia; conventional (typical) antipsychotic agents appear to have lesser effects on negative manifestations of the disorder. In comparative studies, clozapine was at least as effective as, or more effective than several conventional antipsychotic agents, including chlorpromazine, haloperidol, perphenazine, or trifluoperazine.

Unlike conventional antipsychotic agents, however, clozapine generally does not induce extrapyramidal effects and has not been clearly implicated as a causative agent in tardive dyskinesia.

While the risks of adverse neurologic effects with long-term clozapine therapy remain to be fully elucidated, other adverse effects, including some potentially serious effects (e.g., agranulocytosis, seizures), may occur more frequently with clozapine therapy. Consequently, the manufacturers and most clinicians currently state that use of clozapine should be reserved for patients with severe disease that fails to respond adequately to conventional antipsychotic therapy, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. What constitutes an adequate trial of standard antipsychotic therapy, however, varies widely. The manufacturers and some clinicians recommend that a patient be given an adequate trial of at least 2 different antipsychotic agents from at least 2 different chemical classes (e.g., phenothiazines, butyrophenones, thioxanthenes) before the patient is considered a candidate for clozapine therapy. The American Psychiatric Association (APA), however, currently recommends that a trial of clozapine be considered in patients who fail to respond to adequate trials of at least one antipsychotic agent unless therapy with the drug is specifically contraindicated (e.g., patients with myeloproliferative disorders, preexisting bone marrow depression, or a history of clozapine-induced agranulocytosis or severe granulocytopenia) or patients are unable or unwilling to comply with monitoring requirements. The APA also recommends that clo-