ARIPIPRAZOLE

0.0 Overview
1) Class
   a) This drug is a member of the following class(es):
      Antipsychotic
2) Dosing Information
   a) Adult
      1) Bipolar disorder, acute, acute manic or mixed episodes
         a) 30 mg ORALLY once daily (may be decreased to 15 mg/day based on tolerability) (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006)
      2) Bipolar disorder - Psychomotor agitation
         a) initial, 9.75 mg IM (dose range 5.25 mg to 15 mg); cumulative doses up to a total of 30 mg/day may be given if a second dose is required; if second dose required, wait at least 2 h after initial dose; for ongoing therapy, oral aripiprazole in a range of 10 mg to 30 mg/day should replace aripiprazole injection as soon as possible (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006)
      3) Psychomotor agitation - Schizophrenia
         a) INTRAMUSCULAR; initial, 9.75 mg IM (dose range 5.25 mg to 15 mg); cumulative doses up to a total of 30 mg/day may be given if a second dose is required; if second dose required, wait at least 2 h after initial dose; for ongoing therapy, oral aripiprazole in a range of 10 mg to 30 mg/day should replace aripiprazole injection as soon as possible (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006)
      4) Schizophrenia
         a) initial, 10 to 15 mg ORALLY once daily, with or without food (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006)
         b) maintenance, MAX daily dosage is 30 mg/day ORALLY; increase dose only after 2 weeks at each dose strength; efficacy has not been significantly greater with doses higher than 10 to 15 mg/day (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006)
   b) Pediatric
      1) safety and efficacy not established in pediatric and adolescent patients (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006)
3) Contraindications
   a) hypersensitivity to aripiprazole or any component of the product (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
4) Serious Adverse Effects
   a) Diabetic ketoacidosis
   b) Neuroleptic malignant syndrome
   c) Orthostatic hypotension
   d) Seizure
5) Clinical Applications
   a) FDA Approved Indications
      1) Bipolar disorder, acute, acute manic or mixed episodes
      2) Bipolar disorder - Psychomotor agitation
      3) Psychomotor agitation - Schizophrenia
      4) Schizophrenia

1.0 Dosing Information
Drug Properties
Storage and Stability
Adult Dosage
Pediatric Dosage

1.1 Drug Properties
A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)
B) Synonyms
   Aripiprazole
C) Physicochemical Properties
   1) Molecular Weight
      a) 448.38 (Prod Info Abilify™, 2002)
1.2 Storage and Stability
A) Oral route
  1) Solution
    a) Aripiprazole oral solution should be stored at 25 degrees Celsius (77 degrees Fahrenheit) with excursions permitted between 15 and 30 degrees Celsius (59 and 86 degrees Fahrenheit). The oral solution should be used within 6 months after opening, but not beyond the expiration date on the bottle (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).
  2) Tablet/Tablet, Disintegrating
    a) Aripiprazole tablets should be stored at 25 degrees Celsius (77 degrees Fahrenheit) with excursions permitted between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.3 Adult Dosage

1.3.1 Normal Dosage

1.3.1.A Intramuscular route

Bipolar disorder - Psychomotor agitation
Psychomotor agitation - Schizophrenia

1.3.1.A.1 Bipolar disorder - Psychomotor agitation
  a) The recommended dose to control agitation in patients with schizophrenia or bipolar mania is 9.75 milligrams (mg) intramuscularly (dose range 5.25 mg to 15 mg). No additional benefit was observed after a 15 mg dose compared to a 9.75 mg dose. Cumulative doses up to a total of 30 mg per day may be administered if a second dose is required. However, the efficacy of repeated doses in agitated patients has not been systematically evaluated in clinical trials. Additionally, the safety of total daily doses greater than 30 mg or injections administered more frequently than every 2 hours have not been adequately evaluated. For ongoing therapy, oral aripiprazole in a range of 10 mg to 30 mg per day should replace aripiprazole injection as soon as possible (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

1.3.1.A.2 Psychomotor agitation - Schizophrenia
  a) The recommended dose to control agitation in patients with schizophrenia is 9.75 milligrams (mg) intramuscularly (dose range 5.25 mg to 15 mg). No additional benefit was observed after a 15 mg dose compared to a 9.75 mg dose. Cumulative doses up to a total of 30 mg per day may be administered if a second dose is required. However, the efficacy of repeated doses in agitated patients has not been systematically evaluated in clinical trials. Additionally, the safety of total daily doses greater than 30 mg or injections administered more frequently than every 2 hours have not been adequately evaluated. For ongoing therapy, oral aripiprazole in a range of 10 mg to 30 mg per day should replace aripiprazole injection as soon as possible (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

1.3.1.B Oral route

Bipolar disorder, acute, acute manic or mixed episodes
Schizophrenia

1.3.1.B.1 Bipolar disorder, acute, acute manic or mixed episodes
  a) In clinical trials, the initial dose of aripiprazole used for the treatment of BIPOLAR MANIA was 30 milligrams (mg) once daily, and this dose was proven to be effective. Based on tolerability, approximately 15% of patient doses were decreased to 15 mg/day. The safety of doses higher than 30 mg/day have not been studied (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).
  b) MAINTENANCE THERAPY
    1) Aripiprazole has been efficacious for stabilizing and maintaining patients with a recent manic or mixed episode for at least 6 weeks. The long-term usefulness for the individual patient should be re-evaluated periodically if therapy is continued for extended periods (longer than 6 weeks) (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.3.1.B.2 Schizophrenia
  a) The recommended initial and target oral dose of aripiprazole for the treatment of schizophrenia is 10 or 15 milligrams (mg) to be given orally once daily, with or without meals (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006). Oral doses of 10 to 30 mg daily have been effective in patients with acutely relapsed schizophrenia or...
schizoaffective disorder (Kane et al, 2000b; Anon, 2000c; Saha et al, 1999b; Petrie et al, 1998a). However, in clinical trials efficacy has not been significantly greater with doses higher than 10 or 15 mg daily. Dose adjustments not should be made before 2 weeks at each dose strength (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

b) Doses of 30 mg daily could be administered without dose titration in one study (Petrie et al, 1998a).

c) MAINTENANCE THERAPY

1) It is unclear how long a patient should remain on aripiprazole therapy; however, patients who had been symptomatically stable on other antipsychotic medications for at least 3 months and were discontinued from those medication and given aripiprazole 15 milligrams daily for up to 26 weeks did demonstrate a benefit from maintenance treatment. Patients should be reassessed at regular intervals to determine the need for ongoing treatment (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

2) Doses of 30 mg daily could be administered without dose titration in one study (Petrie et al, 1998a).

d) SWITCHING FROM OTHER ANTIPSYCHOTICS

1) Data are not available to recommend guidelines for switching from other antipsychotics to aripiprazole or for concomitant administration with other antipsychotics. The previous antipsychotic treatment may be immediately discontinued or more gradually discontinued, depending on the individual patient. However, in all cases, duration of antipsychotic administration overlap should be kept to a minimum (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.3.1.8.3 ORAL SOLUTION

a) Dosages for the aripiprazole oral solution may be substituted for the tablet dosages on a milligram-per-milligram (mg) basis for the 5, 10, 15, or 20 mg tablets (up to a 25 mg dose). Patients receiving 30 mg tablets should receive 25 mg of the oral solution (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

b) Patients using the oral solution should be advised that every milliliter (mL) of aripiprazole oral solution contains sucrose 400 milligrams (mg) and fructose 200 mg (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.3.1.8.4 SPECIAL DOSING CONSIDERATIONS

a) The dosage of aripiprazole should be reduced to one-half the usual dose when administered concurrently with potential CYP3A4 inhibitors (ie, ketoconazole). When the CYP3A4 inhibitor is discontinued from the combination therapy, the aripiprazole dose should be increased (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

b) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administered concurrently with potential CYP2D6 inhibitors (ie, quinidine, fluoxetine, or paroxetine). When the CYP2D6 inhibitor is discontinued from the combination therapy, the aripiprazole dose should be increased (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

c) When taken concomitantly with a potential CYP3A4 inducer (ie, carbamazepine), the dose of aripiprazole should be doubled to 20 or 30 milligrams (mg). Additional increases in dose should occur based on clinical evaluation. When the CYP3A4 inducer is withdrawn from combination therapy, the aripiprazole dose should be reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

d) Aripiprazole oral tablet dosages may be substituted with the oral solution on a mg-per-mg basis for the 5-, 10-, 15-, or 20-mg tablets up to a dose of 25 mg. The 30-mg tablet strength should be replaced by 25 mg of the solution (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.3.2 Dosage in Renal Failure

A) Dosage adjustment is not required (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.3.3 Dosage in Hepatic Insufficiency

A) Dosage adjustment is not required (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.3.4 Dosage in Geriatric Patients

A) Dosage adjustment is not required (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.3.6 Dosage in Other Disease States

A) The dosage of aripiprazole should be reduced to one-half the usual dose when administered concurrently with potential CYP3A4 inhibitors, such as ketoconazole. When the CYP3A4 inhibitor is discontinued from the combination therapy, the aripiprazole dose should be increased (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

B) The dosage of aripiprazole should be reduced to at least one-half the usual dose when administered concurrently with potential CYP2D6 inhibitors, such as quinidine, fluoxetine, or paroxetine. When the CYP2D6 inhibitor is discontinued from the combination therapy, the aripiprazole dose should be increased (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

C) The dosage of aripiprazole should be doubled to 20 or 30 milligrams (mg) when administered concurrently with a potential CYP3A4 inducer, such as carbamazepine. Additional increases in dose should occur based on clinical evaluation. When the CYP3A4 inducer is withdrawn from combination therapy, the aripiprazole dose should be reduced to 10 to 15 mg (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

D) Aripiprazole oral tablet dosages may be substituted with the oral solution on a mg-per-mg basis for the 5-, 10-, 15-, or 20-mg tablets up to a dose of 25 mg. The 30-mg tablet strength should be replaced by 25 mg of the solution (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).

1.4 Pediatric Dosage

1.4.1 Normal Dosage

1.4.1.1 Oral route

1) The safety and efficacy of aripiprazole have not been established in pediatric and adolescent patients (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).
2.0 Pharmacokinetics

2.1 Onset and Duration

A) Onset
1) Initial Response
   a) SCHIZOPHRENIA, ORAL: 1 week (10 to 30 mg daily) (Petrie et al, 1998b; Anon, 2000b).
   b) In phase II studies involving hospitalized schizophrenic patients, significant improvement (including negative symptoms) was seen after one week of therapy with aripiprazole 30 mg daily. With lower doses (2 or 10 mg daily), symptom improvement was not seen until week 2 or 3, and benefits were less substantial (Petrie et al, 1998b).

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration
1) Not established.

B) Peak Concentration
1) Following an intramuscular dose, the geometric mean maximum concentration (Cmax) was on average 19% higher than the Cmax after an oral tablet administration (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

C) Time to Peak Concentration
1) Oral: 3 to 5 hours (Anon, 2000b; Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).
2) Intramuscular: 1 to 3 hours (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006)
   a) In healthy subjects receiving once-daily doses of 5 and 20 mg, mean peak plasma levels on day 14 were 77 and 302 ng/mL, respectively, and occurred in 3 to 5 hours (Anon, 2000b).
   b) With a titrated dosing schedule of 10 mg daily for 2 days, then 20 mg daily for 2 days, and finally 30 mg daily for 10 days, the mean peak plasma concentration on day 14 was 452 ng/mL (3 hours) (Anon, 2000b).
   c) In 2 studies of healthy subjects, the median times to peak plasma concentrations following intramuscular aripiprazole administrations were 1 and 3 hours (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

D) Area Under the Curve
1) The aripiprazole area under the curve (AUC) in the first 2 hours after an intramuscular injection was 90% greater than the AUC after the same dose as a tablet; however, both routes had similar systemic exposure over 24 hours. When intramuscular aripiprazole doses were administered to stable patients with schizophrenia or schizoaffective disorder, the pharmacokinetics of aripiprazole were linear over a dose range of 1 to 45 mg (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

2.3 ADME

Absorption
Distribution
Metabolism
Excretion
Elimination Half-life

2.3.1 Absorption

A) Bioavailability
1) Oral: tablet, 87%; solution, well-absorbed (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).
2) Intramuscular: 100% after a 5-mg intramuscular injection (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).
   a) A comparative bioavailability study which compared the pharmacokinetics of a 30 milligram aripiprazole tablet with 30 milligrams of the oral solution found that plasma concentrations of aripiprazole were higher with the solution than with the tablet. In healthy subjects, mean maximum plasma concentration and area under the curve values were 22% and 14% higher with the solution as compared with the tablet formulation (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).
   b) Pharmacokinetic studies with the orally disintegrating aripiprazole tablet indicate that they are bioequivalent to aripiprazole tablets (Prod Info ABILIFY(R) DISCMELT(TM) orally disintegrating tablets, 2006).

B) Effects of Food
1) Absorption unaffected (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).
   a) Peak serum levels and AUC of aripiprazole and dehydroaripiprazole are not significantly affected when aripiprazole is given with food. The time to peak serum levels is delayed (by 3 hours for aripiprazole and by 12 hours for dehydroaripiprazole) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

2.3.2 Distribution

A) Distribution Sites
1) Protein Binding
2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver, extent unknown (Lawler et al., 1999).
   a) Metabolic pathways include dehydrogenation and hydroxylation (via cytochrome P450 (CYP)-3A4 and CYP-2D6); N-dealkylation also occurs via CYP-3A4. Aripiprazole is the primary compound in plasma. Aripiprazole does not inhibit or induce the CYP-2D6 pathway (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

   b) Poor metabolizers (CYP-2D6) have been identified (speculated as 8% of population); these patients have an approximate 60% greater exposure to active compounds (aripiprazole and dehydroaripiprazole). Inhibitors of CYP-2D6 are capable of increasing aripiprazole plasma levels significantly (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

B) Metabolites
1) Dehydroaripiprazole (active) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).
   a) Major metabolite, representing about 40% of aripiprazole AUC in plasma. This metabolite has affinities for D2 receptors similar to the parent compound and appears to contribute to pharmacologic activity (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

2.3.4 Excretion
A) Kidney
1) Renal Excretion (%)
   a) 25% of dose (less than 1% unchanged aripiprazole) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

B) Feces
1) FECES, 55% of a dose (about 18% unchanged aripiprazole) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

2.3.5 Elimination Half-life
A) Parent Compound
1) ELIMINATION HALF-LIFE
   a) 75 hours (extensive metabolizers) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

   b) An elimination half-life of 146 hours has been reported in poor metabolizers (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

B) Metabolites
1) Dehydroaripiprazole, 94 hours (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

3.0 Cautions

3.1 Contraindications
A) hypersensitivity to aripiprazole or any component of the product (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)

3.2 Precautions
A) elderly patients with dementia (unapproved use); increased risk of death (1.6 to 1.7 times greater than placebo) reported when atypical antipsychotics were used off-label to treat behavioral disorders associated with dementia; most deaths were attributed to cardiovascular events (e.g., heart failure or sudden death) or infections (mostly pneumonia) (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)

B) aspiration pneumonia, at-risk patients; esophageal dysmotility and aspiration have been reported, especially in the elderly and those with advanced Alzheimer's dementia (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
3.3 Adverse Reactions

Cardiovascular Effects
Endocrine/Metabolic Effects
Gastrointestinal Effects
Neurologic Effects
Ophthalmic Effects
Psychiatric Effects
Renal Effects
Other

3.3.1 Cardiovascular Effects

Orthostatic hypotension

3.3.1.A Cardiovascular finding

1) Slight increases in heart rate or tachycardia have occurred in some patients (Prod Info Abilify(TM), 2002c). Prolongation of the QT-interval has been observed rarely (Prod Info Abilify(TM), 2002c). The safety of aripiprazole has not been assessed in patients with preexisting cardiovascular disease, or those with risk factors for torsades de pointes.

2) An increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, has been associated with the use of aripiprazole in elderly patients with dementia-related psychosis when compared with placebo. Safety and efficacy have not been established in the treatment of patients with psychosis associated with dementia (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.1.B Orthostatic hypotension

1) Incidence: 0.7% to 1.9%

2) Orthostatic hypotension has been reported in about 2% of schizophrenic patients receiving aripiprazole (1% placebo), and approximately 0.7% of bipolar patients (0% placebo). Incidences of orthostatic light-headedness and syncope were not different from placebo (about 0.5 to 1%) (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.3 Endocrine/Metabolic Effects

Diabetic ketoacidosis

3.3.3.A Diabetic ketoacidosis

1) A case of new-onset diabetes and diabetic ketoacidosis with elevated lipase was described in a 33-year-old, schizophrenic, African-American man following treatment with aripiprazole. Prior to current presentation, the patient had been on aripiprazole therapy for 18 months (dose was not available) and had a body mass index (BMI) was 32 kilogram/square meters (kg/m(2)) prior to taking aripiprazole. At the time of presentation, the patient had symptoms of fatigue, dyspepsia, and epigastric abdominal pain. The patient had progressively gained weight since initiating aripiprazole treatment and his current BMI was 41 kg/m(2). Laboratory tests indicated hyperglycemia (blood glucose of 1,769 milligrams/deciliter (mg/dL)), diabetic ketoacidosis (anion gap of 32 millimoles (mmol)/L, serum osmolality of 373 milliosmoles/kg, CO2 of 6 mmol/L), and hyperlipasemia (lipase of 4,068 International Units/L). An abdominal ultrasound and CT scan were negative for pancreatitis and gallstones, and thyroid function tests were normal. The patient did not have a prior medical history or a family history of diabetes mellitus. Aripiprazole was discontinued and the patient was treated with intravenous fluids and insulin. A diagnosis of aripiprazole-
induced diabetes and elevated lipase, secondary to diabetic ketoacidosis, was made and the patient was discharged home with haloperidol and insulin glargine. Six months after discontinuation of aripiprazole, the patient's BMI had decreased to 33 kg/m(2) and, while still diabetic, his insulin requirements were reduced. It was proposed that patients' weight and blood glucose may need be monitored during aripiprazole therapy (Reddymasu et al, 2006).

3.3.3.B Endocrine finding

1) Serum prolactin levels have been unaffected or increased only slightly by oral aripiprazole (2 to 30 mg daily) in schizophrenic patients (Anon, 2000a; Petrie et al, 1998; Kane et al, 2000a). Increases in prolactin levels were greater with haloperidol 10 mg daily in comparative studies (Kane et al, 2000a; Saha et al, 1999a).

3.3.3.C Hyperglycemia

1) Hyperglycemia has been reported in patients treated with atypical antipsychotics; and in some instances it has been extreme and associated with ketoacidosis, hyperosmolar coma or death. There have been few reports of hyperglycemia in patients treated with aripiprazole. The relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Because aripiprazole was not marketed at the time these studies were conducted, it is not known if aripiprazole is associated with this increased risk (Prod Info Abilify(TM), 2004).

3.3.3.D Weight gain

1) Incidence: up to 30% (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006)
2) Weight gain has been reported during aripiprazole therapy, although the incidence was less than with haloperidol (Anon, 2000a; Saha et al, 1999a; Kane et al, 2000a).
3) Weight gain has been observed among patients treated with aripiprazole (dose range, 5 to 30 milligrams (mg) per day) for schizophrenia (+0.7 kilograms (kg) vs -0.05 kg placebo) in 4- to 6-week trials. A larger proportion of patients (8%) receiving aripiprazole group relative to placebo (3%) also gained 7% or greater body weight from baseline (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006).
4) In one large 4-week study, weight gain of more than 7% was observed in about 11% of patients treated with aripiprazole 2 to 30 mg daily (no dose-relationship) and 14% receiving haloperidol 10 mg daily (Saha et al, 1999a).
5) In a 26-week, placebo-controlled trial among patients treated with aripiprazole 15 mg daily for schizophrenia, proportions of patients who gained 7% or greater body weight from baseline were as followed (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006):

<table>
<thead>
<tr>
<th>Body-Mass Index (BMI)</th>
<th>Aripiprazole</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 23</td>
<td>6.8%</td>
<td>3.7%</td>
</tr>
<tr>
<td>23 to 27</td>
<td>5.1%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Greater than 27</td>
<td>5.7%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

p values not provided
6) In a 52-week, active-controlled trial with aripiprazole for schizophrenia, weight changes from baseline were shown below (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006):

<table>
<thead>
<tr>
<th>Body-Mass Index (BMI)</th>
<th>Mean weight change from baseline (kilograms)</th>
<th>Weight gain of 7% or greater from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 23</td>
<td>2.6</td>
<td>30%</td>
</tr>
<tr>
<td>23 to 27</td>
<td>1.4</td>
<td>19%</td>
</tr>
<tr>
<td>Greater than 27</td>
<td>-1.2</td>
<td>8%</td>
</tr>
</tbody>
</table>

p values not provided

3.3.4 Gastrointestinal Effects

Constipation
Nausea
Vomiting

3.3.4.A Constipation

1) Incidence: 11% (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
2) In a pooled analysis of schizophrenic and bipolar patients, constipation was reported in 11% of patients receiving aripiprazole (doses 2 mg/day or greater) compared with 7% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.4.B Nausea

1) Incidence: 16% (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
2) In a pooled analysis of schizophrenic and bipolar patients, nausea was reported in 16% of patients receiving aripiprazole (doses 2 mg/day or greater) compared with 12% of
7 patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.4.C Vomiting
1) Incidence: 12% (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
2) In a pooled analysis of schizophrenic and bipolar patients, vomiting was reported in 12% of patients receiving aripiprazole (doses 2 mg/day or greater) compared with 6% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.9 Neurologic Effects

Akathisia
Extrapyramidal sign
Headache
Insomnia
Lethargy
Neuroleptic malignant syndrome
Seizure
Somnolence

3.3.9.A Akathisia
1) Incidence: 8% to 10% (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
2) In five short-term, placebo-controlled trials of patients with schizophrenia, 8% of patients receiving aripiprazole (2 to 30 mg/day) experienced akathisia compared with 4% of the placebo group (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).
3) In a pooled analysis of schizophrenic and bipolar patients, akathisia was reported in 10% of patients receiving aripiprazole (doses 2 mg/day or greater) compared with 4% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.9.B Extrapyramidal sign
1) A case report described the development of extrapyramidal symptoms (EPS) in a 56-year-old schizophrenic woman following treatment with aripiprazole. The patient, who presented with psychiatric symptoms of paranoid and persecutory delusions, auditory hallucinations, and perplexed mood, was started on aripiprazole 10 mg once daily. The dose was increased to 15 mg once daily the second week and then to 30 mg once daily the third week. Five weeks after the initiation of aripiprazole, including 3 weeks at the 30 mg dose, the patient developed stiffness of the trunk and limbs, parkinsonian-gait, mask-like facial expression, and hypersalivation. None of these symptoms had been documented in this patient prior to aripiprazole therapy, and the patient had not received treatment with any other antipsychotic agents previously. Akathisia was absent, and acute dystonia was ruled out based on absence of opisthotonos, torticollis, oculogyric crisis, and the time of onset. Subsequently, the aripiprazole dose was reduced to 15 mg daily and procyclidine 5 mg was added, which prompted resolution of the stiffness. However, the patient continued to hypersalivate and her psychotic symptoms did not improve. Aripiprazole treatment was stopped 7 days after the onset of EPS and nightly olanzapine therapy was initiated, starting with 2.5 mg for 3 days, followed by 5 mg thereafter. The hypersalivation resolved 10 days after discontinuation of aripiprazole and no further EPS symptoms were observed. While the exact mechanism for this adverse event was not elucidated, an idiosyncratic reaction to aripiprazole, rather than a general side effect, was postulated as a possible cause for this effect (Salmoiraghi & Odiyoor, 2006).
2) Extrapyramidal symptoms have been minimal during oral aripiprazole therapy of schizophrenia in unpublished studies (Kane et al, 2000a; Saha et al, 1999a; Petrie et al, 1998; Inoue & Nakata, 2001a). In one 4-week study, the overall incidence of extrapyramidal side effects with aripiprazole 15 or 30 mg daily was similar to that in the placebo group; at least one dose of benztropine was required in 11 to 17% of patients receiving these doses of aripiprazole, compared to 36% assigned to haloperidol 10 mg daily (Kane et al, 2000a). The frequency of extrapyramidal symptoms was also lower with aripiprazole than haloperidol in a phase II study (Saha et al, 1999a).
3) Collective study data from the manufacturer indicates an overall incidence of extrapyramidal symptoms of 6% with both aripiprazole and placebo. Akathisia, however, has occurred slightly more often aripiprazole (3%) (Prod Info Abilify(TM), 2002c).

3.3.9.C Headache
1) Incidence: 30% (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
2) In a pooled analysis of schizophrenic and bipolar patients, headache was reported in 30% of patients receiving aripiprazole (doses 2 mg/day or greater) compared with 25% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.9.D Insomnia
1) Incidence: 19% (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
2) In a pooled analysis of schizophrenic and bipolar patients, insomnia was reported in 19% of patients receiving aripiprazole (doses 2 mg/day or greater) compared with 14% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.9.E Lethargy
1) Incidence: 5% (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
2) During three, 10-week controlled trials of 938 elderly patients (mean age: 82.4 years) with Alzheimer's disease and related psychosis, lethargy was reported in 5% of patients receiving aripiprazole, compared with 2% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).
3.3.9.F  Neuroleptic malignant syndrome
   1) Incidence: rare (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
   2) Neuroleptic malignant syndrome has been reported rarely in the worldwide clinical database in patients on aripiprazole therapy (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.9.G  Seizure
   1) Incidence: rare (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
   2) Seizures were reported in approximately 0.1% (1/926) of schizophrenic patients receiving aripiprazole. Seizures were reported in approximately 0.3% (2/597) of bipolar patients receiving aripiprazole and 0.2% (1/436) of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.9.H  Somnolence
   1) Incidence: 10% to 14% (Prod Info ABILIFY(R) tablets, oral solution, 2004)
   2) Somnolence was reported in 10% of schizophrenic patients receiving aripiprazole and 8% of patients receiving placebo. Somnolence led to discontinuation of therapy in 0.1% (1/926) of patients. In patients treated for bipolar disorder, somnolence was reported in 14% receiving aripiprazole and 7% receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).
   3) Excessive somnolence requiring hospitalization was observed in a 9-year-old girl weighing 25 kilograms (kg) within 3.5 hours of initiation of aripiprazole at a dose of 15 milligrams (mg)/day (0.6 mg/kg/day) for the treatment of oppositional defiant disorder. Although optimal dosing in pediatric patients has not been established, this dose is up to three times higher than doses used in a clinical study including children of similar body weight to this patient (ie, 0.2 mg/kg/day or 2 to 5 mg/day) (Davenport et al, 2004).
   4) During three, 10-week controlled trials of 938 elderly patients (mean age: 82.4 years) with Alzheimer's disease and related psychosis, somnolence (including sedation) was reported in 8% of patients receiving aripiprazole, compared with 3% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.10  Ophthalmic Effects

3.3.10.A  Blurred vision
   1) Incidence: 3% (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
   2) In a pooled analysis of schizophrenic and bipolar patients, blurred vision was reported in 3% of patients receiving aripiprazole (doses 2 mg/day or greater) compared with 1% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.12  Psychiatric Effects

3.3.12.A  Anxiety
   1) Incidence: 20% (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
   2) In a pooled analysis of schizophrenic and bipolar patients, anxiety was reported in 20% of patients receiving aripiprazole (doses 2 mg/day or greater) compared with 17% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.13  Renal Effects

3.3.13.A  Incontinence
   1) Incidence: 5% (Prod Info ABILIFY(R) oral tablets, oral solution, 2006)
   2) During three, 10-week controlled trials of 938 elderly patients (mean age: 82.4 years) with Alzheimer's disease and related psychosis, incontinence (primarily urinary) was reported in 5% of patients receiving aripiprazole, compared with 1% of patients receiving placebo (Prod Info ABILIFY(R) oral tablets, oral solution, 2006).

3.3.16  Other

3.3.16.A  Dead
   1) The findings of one meta-analysis suggest that there may be a small increased risk of death associated with the use of atypical antipsychotic agents for the treatment of dementia in elderly patients. The study analysis (n=5110), including 15 randomized, double-blind, placebo-controlled, parallel group trials of antipsychotic use (ie, aripiprazole (n=3), olanzapine (n=5), quetiapine (n=3), risperidone (n=5)) in elderly patients (weighted mean age, 81.2 years) with dementia, found that death occurred more often in patients receiving atypical antipsychotic therapy as compared with placebo (118 (3.5%) vs 40 (2.3%), respectively). The overall odds ratio, as assessed by meta-analysis, for death in elderly patients receiving antipsychotics as compared with placebo was 1.54 (95% CI= 1.06 to 2.23; p=0.02), and the risk difference was 0.01 (95% CI= 0.004 to 0.02; p=0.01). Overall, the relative risk associated with atypical antipsychotic use was 1.65 (95% CI= 1.19 to 2.29; p=0.003); however this increased risk was only identified when all drugs were pooled for analysis; meta-analyses of individual drugs did not show a statistically significant increased risk. A similar drop-out rate was observed between antipsychotic- and placebo-treated patients (32.2% vs 31.4%, respectively), with no significant difference in drop-outs found by meta-analysis (Schneider et al, 2005).
   2) The results of a retrospective cohort study indicate that conventional antipsychotic agents are at least as likely as atypical antipsychotic agents to increase the risk of death among elderly patients 65 years of age or older. The study included 9,142 new users of conventional agents (mean age, 83.2 years) and 13,748 new users of atypical agents (mean age, 83.2 years).
A higher adjusted relative risk of death was associated with the use of conventional antipsychotics as compared with atypical antipsychotics at all time points studied after beginning therapy (within 180 days: RR, 1.37; 95% CI=1.27 to 1.49; less than 40 days: RR, 1.56; 95% CI=1.37 to 1.78; 40 to 79 days: RR, 1.37; 95% CI=1.19 to 1.59; 80 to 180 days: RR, 1.27; 95% CI=1.14 to 1.41). In addition, the adjusted risks of death observed in patients with dementia (RR, 1.29; 95% CI=1.15 to 1.45), without dementia (RR, 1.45; 95% CI=1.30 to 1.63), in a nursing home (RR, 1.26; 95% CI=1.08 to 1.47), or not in a nursing home (RR, 1.42; 95% CI=1.29 to 1.56) were also higher with the use of conventional antipsychotic therapy as compared with atypical antipsychotic use. This risk appeared to be dose-related and was greater with the use of higher dose (ie, greater than the median) conventional antipsychotics (RR, 1.73; 95% CI=1.57 to 1.90). Additional studies which specifically investigate the optimum care of elderly patients requiring antipsychotic therapy are needed so that appropriate guidance regarding therapeutic intervention can be provided (Wang et al, 2005).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding

A) Teratogenicity/Effects in Pregnancy

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Abilify(TM), 2002) (All Trimesters)
   a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management
   a) There is insufficient clinical experience with the use of aripiprazole in pregnancy to confirm its safety in that patient population. A case report described a successful outcome in a 27-year-old, schizoaffective woman who was treated with aripiprazole during different trimesters (Mendhekar et al, 2006). According to the manufacturer, aripiprazole was teratogenic and fetotoxic in animal studies (Prod Info Abilify(TM), 2002). Until additional data are available, caution should be exercised with aripiprazole use pregnant women.

4) Literature Reports
   a) In the case of a 27-year-old, medically healthy, schizoaffective woman, exposure to aripiprazole during different trimesters of pregnancy was not associated with fetal toxicity. The patient was being effectively treated with aripiprazole 15 mg/day when she conceived. At week 8 of gestation, aripiprazole was withdrawn following a risk-to-benefit analysis. However, at week 20 of gestation, the patient suffered a schizophrenic relapse and following a revised risk-to-benefit analysis, aripiprazole was re-initiated at a 10 mg/day dose which was continued throughout the pregnancy. The patient's overall weight gain at full term was 10 kg. Ultrasound scans and laboratory tests for serum glucose, thyroid function, and routine hematology during the pregnancy were normal. Although spontaneous labor occurred at term, development of unexplained fetal distress in the form of tachycardia prompted a cesarean section which resulted in the birth of a male infant weighing 3.25 kg. Failure to establish lactation led to the infant being bottle-fed from birth. At the 6 month follow-up, the infant had achieved normal milestones (Mendhekar et al, 2006).

B) Breastfeeding

1) Thomson Lactation Rating: Infant risk cannot be ruled out.
   a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

2) Clinical Management
   a) It is not known whether aripiprazole is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown. It is not known if aripiprazole affects the quantity or composition of breastmilk. According to the manufacturer, aripiprazole was excreted into the milk of lactating rats (Prod Info Abilify(TM), 2002a).

3) Literature Reports
   a) No reports describing the use of aripiprazole during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.

4) Drug Levels in Breastmilk
   a) Active Metabolites
      1) dehydro-aripiprazole (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006)

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Carbamazepine
Fluoxetine
Itraconazole
Ketoconazole
Paroxetine
Quinidine
Ranolazine

3.5.1.A Carbamazepine
1) Interaction Effect: decreased aripiprazole concentrations
2) Summary: Coadministration of carbamazepine 200 milligrams (mg) twice daily with aripiprazole 30 mg once daily decreased the maximum concentration (Cmax) and the area under the concentration-time curve (AUC) values of both aripiprazole and its active metabolite, dehydro-aripiprazole, by approximately 70%. Aripiprazole is partly metabolized by
cytochrome P450 3A4 (CYP3A4) enzymes. Coadministration with carbamazepine, a potent CYP3A4 inducer, could increase aripiprazole clearance causing decreased blood concentrations. The dose of aripiprazole should be doubled when it is administered concurrently with carbamazepine. If therapy with carbamazepine is discontinued, the dose of aripiprazole should then be decreased (Prod Info ABILIFY(R) oral tablets, oral solution, 2005).

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of aripiprazole and carbamazepine has resulted in decreased aripiprazole concentrations. The dose of aripiprazole should be doubled when it is administered concurrently with carbamazepine. If therapy with carbamazepine is discontinued, the dose of aripiprazole should then be decreased.
7) Probable Mechanism: induction of CYP3A4-mediated aripiprazole metabolism

3.5.1.1 Fluoxetine
1) Interaction Effect: increased aripiprazole levels
2) Summary: Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministration with CYP2D6 inhibitors, such as fluoxetine, may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with fluoxetine is discontinued, the dose of aripiprazole should then be increased (Prod Info ABILIFY(R) oral tablets, oral solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with fluoxetine. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with fluoxetine is discontinued, the dose of aripiprazole should then be increased.
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of aripiprazole

3.5.1.2 Itraconazole
1) Interaction Effect: increased aripiprazole concentrations
2) Summary: Coadministration of ketoconazole 200 milligrams (mg) per day for 14 days with a single 15 mg aripiprazole dose increased area under the concentration-time curve (AUC) values of both aripiprazole and its active metabolite, dehydro-aripiprazole, by 63% and 77%, respectively. Aripiprazole is partly metabolized by cytochrome P450 3A4 (CYP3A4) enzymes. Ketoconazole, a potent CYP3A4 inhibitor, could inhibit aripiprazole elimination resulting in increased blood concentrations. Coadministration of aripiprazole with itraconazole, also a strong CYP3A4 inhibitor, may result in a similar effect. Consider reducing aripiprazole dose by one-half when these agents are coadministered. If therapy with itraconazole is discontinued, the dose of aripiprazole should then be increased.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with itraconazole. Consider reducing aripiprazole dose by approximately one-half when these agents are coadministered. If therapy with itraconazole is discontinued, the dose of aripiprazole should then be increased.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated metabolism of aripiprazole

3.5.1.3 Ketoconazole
1) Interaction Effect: increased aripiprazole concentrations
2) Summary: Coadministration of ketoconazole 200 milligrams (mg) daily for 14 days with a single 15 mg aripiprazole dose resulted in increased area under the concentration-time curve (AUC) values of both aripiprazole and its active metabolite, dehydro-aripiprazole, by 63% and 77%, respectively. Aripiprazole is partly metabolized by cytochrome P450 3A4 (CYP3A4) enzymes. Coadministration with ketoconazole, a potent CYP3A4 inhibitor, could inhibit aripiprazole elimination resulting in increased blood concentrations. Reduce the aripiprazole dose to one-half of its normal dose when these agents are coadministered. If therapy with ketoconazole is discontinued, the dose of aripiprazole should then be increased.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of aripiprazole and ketoconazole has resulted in increased aripiprazole concentrations. Reduce the aripiprazole dose to one-half of its normal dose when these agents are coadministered. If therapy with ketoconazole is discontinued, the dose of aripiprazole should then be increased.
7) Probable Mechanism: inhibition of CYP3A4-mediated aripiprazole metabolism

3.5.1.4 Paroxetine
1) Interaction Effect: increased aripiprazole levels
2) Summary: Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministration with CYP2D6 inhibitors, such as paroxetine, may inhibit aripiprazole elimination causing increased blood concentrations. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with paroxetine is discontinued, the dose of aripiprazole should then be increased.
3) Severity: moderate

http://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.PrintReady
12/23/2006
4) Onset: delayed  
5) Substantiation: theoretical  
6) Clinical Management: Increased aripiprazole plasma levels may result if used concomitantly with paroxetine. Consider a dosage reduction for aripiprazole when these agents are coadministered. If therapy with paroxetine is discontinued, the dose of aripiprazole should then be increased.  
7) Probable Mechanism: inhibition of cytochrome P450 2D6-mediated metabolism of aripiprazole

3.5.1.F Quinidine  
1) Interaction Effect: increased aripiprazole levels  
2) Summary: Coadministration of quinidine 166 milligrams (mg) daily for 13 days with a single 10 mg dose of aripiprazole increased the area under the concentration-time curve (AUC) value of aripiprazole by 112% and decreased the AUC of its active metabolite, dehydro-ariipiprazole, by 35%. Aripiprazole is partly metabolized by cytochrome P450 2D6 (CYP2D6) enzymes. Coadministration with quinidine, a potent CYP2D6 inhibitor, could inhibit aripiprazole elimination resulting in increased blood concentrations. Reduce the aripiprazole dose to one-half of its normal dose when these agents are coadministered. If therapy with quinidine is discontinued, the dose of aripiprazole should then be increased (Prod Info ABILIFY(R) oral tablets, oral solution, 2005).  
3) Severity: moderate  
4) Onset: delayed  
5) Substantiation: probable  
6) Clinical Management: Coadministration of aripiprazole and quinidine has resulted in increased aripiprazole concentrations. Reduce the aripiprazole dose to one-half of its normal dose when these agents are coadministered. If therapy with quinidine is discontinued, the dose of aripiprazole should then be increased.  
7) Probable Mechanism: inhibition of CYP2D6-mediated metabolism of aripiprazole

3.5.1.G Ranolazine  
1) Interaction Effect: an increase in aripiprazole serum concentration and an additive effect on QTc prolongation  
2) Summary: Ranolazine, and/or its metabolites, partially inhibit cytochrome P450-2D6-mediated aripiprazole metabolism resulting in increased aripiprazole exposure. Concurrent administration of ranolazine and antipsychotics that could prolong the QTc interval, such as aripiprazole, is contraindicated (Prod Info RANEXA(TM) extended-release tablets, 2006).  
3) Severity: contraindicated  
4) Onset: unspecified  
5) Substantiation: theoretical  
6) Clinical Management: Using ranolazine and aripiprazole together is contraindicated due to the additive effects on QTc prolongation.  
7) Probable Mechanism: ranolazine inhibition of cytochrome P450-2D6-mediated metabolism of aripiprazole

4.0 Clinical Applications  
4.1 Monitoring Parameters  
A) Therapeutic  
1) Physical Findings  
   a) Improvement of schizophrenic symptoms (positive and negative) (ie, PANSS, BPRS monitoring)  
B) Toxic  
1) Laboratory Parameters  
   a) Routine blood chemistry periodically  
2) Physical Findings  
   a) Monitor patients with an established diagnosis of diabetes mellitus for worsening of glucose control during treatment with an atypical antipsychotic. Patients with risk factors for diabetes mellitus (ie, obesity, family history of diabetes) who are beginning treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically throughout treatment (Prod Info Abilify(TM), 2004).  
   b) Monitor patients for signs and symptoms of hyperglycemia (ie, polydipsia, polyuria, polyphagia, and weakness). Patients who exhibit symptoms of hyperglycemia during atypical antipsychotic treatment should undergo fasting blood glucose testing. In some instances, hyperglycemia has resolved when the atypical antipsychotic was stopped; however, some patients required ongoing anti-diabetic treatment despite discontinuation of the suspect medication (Prod Info Abilify(TM), 2004).  
   c) Periodic blood pressure and heart rate determinations, particularly in patients with preexisting cardiovascular disease  
   d) Monitoring for abnormal-movement detection (extrapyramidal symptoms) and early signs of tardive dyskinesia (eg, worm-like tongue movements); therapy discontinuation is indicated at first sign of tardive dyskinesia  
   e) Signs/symptoms of other toxicity, such as persistent nausea, somnolence, postural dizziness, palpitations, micturition disturbances, mood changes, sexual dysfunction, skin rash)
### 4.2 Patient Instructions

**A) ARIPIPRAZOLE (By mouth)**

Aripiprazole

Treats mental illnesses, including schizophrenia and some symptoms of bipolar disorder (manic episodes).

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to aripiprazole.

How to Use This Medicine:

**Liquid, Tablet, Dissolving Tablet**

Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times in order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.

You may take this medicine with or without food.

Measure the medicine with a marked measuring spoon, oral syringe, or medicine cup.

If you are using the oral disintegrating tablet, make sure your hands are dry before you handle the tablet. Do not open the blister pack that contains the tablet until you are ready to take it. Remove the tablet from the blister pack by peeling back the foil, then taking the tablet out. Do not push the tablet through the foil. Place the tablet on your tongue. It should melt quickly. If possible, take the tablet without any liquid. If needed, you may take a sip of water. Do not split the tablet.

If a Dose is Missed:

If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Opened bottles of the oral liquid form can be used for up to 6 months after opening, but not beyond the expiration date on the bottle.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.

Keep all medicine away from children and never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are also using medicine to lower blood pressure. Some blood pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Losartan®, Norvasc®, Toprol®, and Zestril®.

Tell your doctor if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), ketoconazole (Nizoral®), paroxetine (Paxil®), or quinidine.

Tell your doctor if you are also using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have heart disease or low blood pressure. Tell your doctor if you have a history of heart attack, stroke, seizures, drug abuse, alcohol abuse, or if you have ever experienced symptoms of neuroleptic malignant syndrome (NMS) in the past.

This medicine may raise your blood sugar. Tell your doctor if you have diabetes. It may be necessary to measure your blood sugar more often. The oral liquid form of this medicine also contains sugar.

Older adults may be more sensitive to the side effects of this medicine, including stroke. Make sure the doctor knows if the person who will be using this medicine has Alzheimer’s disease. This medicine is not used to treat dementia in older adults.

The oral disintegrating tablet form of this medicine contains phenylalanine. Make sure your doctor knows if you have phenylketonuria (PKU).

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert.

You may get overheated more easily while you are using this medicine. Be careful if you exercise often or are in high heat or humidity. Drink plenty of water every day. Most people should drink at least eight cups (8 ounces per cup) of water per day.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.

Change in how much or how often you urinate.
Chest pain, fast or slow heartbeat.
Confusion, unusual behavior, depressed mood, or thoughts of hurting yourself.
Excessive hunger or thirst, increased urination, and weakness.
Extreme sleepiness or weakness with nausea, vomiting, or diarrhea.
Fever, sweating, confusion, uneven heartbeat, or muscle stiffness.
Lightheadedness or fainting.
Seizures.
Trouble swallowing.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).
Unusual bleeding, bruising, or weakness.

If you notice these less serious side effects, talk with your doctor:
Anxiety, nervousness, restlessness, or trouble sleeping.
Headache or flu symptoms.
Nausea, vomiting, constipation, loss of appetite, or upset stomach.
Runny or stuffy nose.
Unexpected weight gain or loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) ARIPIPRAZOLE (Injection)
Aripiprazole

Treats agitation associated with schizophrenia or bipolar disorder (manic or mixed).

When This Medicine Should Not Be Used:
You should not receive this medicine if you have had an allergic reaction to aripiprazole.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into one of your muscles.
A nurse or other trained health professional will give you this medicine.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are also using medicine to lower blood pressure. Some blood pressure medicines are atenolol, hydrochlorothiazide (HCTZ), lisinopril, metoprolol, quinapril, Accupril®, Cozaar®, Diovan®, Lotrel®, Norvasc®, Toprol®, and Zestril®.
Tell your doctor if you are also using carbamazepine (Tegretol®), fluoxetine (Prozac®), ketoconazole (Nizoral®), paroxetine (Paxil®), or quinidine.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and allergy medicine, narcotic pain relievers, and sedatives.
Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:
Make sure your doctor knows if you are pregnant or breastfeeding, or if you have heart disease or low blood pressure. Tell your doctor if you have a history of heart attack, stroke, seizures, drug abuse, alcohol abuse, or if you have ever experienced symptoms of neuroleptic malignant syndrome (NMS) in the past.
Older adults may be more sensitive to the side effects of this medicine, including stroke. Make sure the doctor knows if the person who will be using this medicine has Alzheimer’s disease. This medicine is not used to treat behavioral problems in older adults with dementia.
This medicine may raise your blood sugar. Tell your doctor if you have diabetes. It may be necessary to measure your blood sugar more often.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. You may also feel lightheaded when standing or sitting up straight, so stand up or sit up slowly.
You may get overheated more easily while you are using this medicine. Be careful if you exercise often or are in high heat or humidity. Drink plenty of water every day. Most people should drink at least eight cups (8 ounces per cup) of water per day.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing.
Change in how much or how often you urinate.
Chest pain, fast or slow heartbeat.
Confusion, unusual behavior, depressed mood, or thoughts of hurting self or others.
Dry mouth, increased thirst or hunger, or muscle cramps.
Fever, sweating, confusion, uneven heartbeat, or muscle stiffness.
Lightheadedness, dizziness, or fainting.
Seizures or tremors.
Severe drowsiness or sleepiness.
Trouble swallowing.
Twitching or muscle movements you cannot control (often in your face, tongue, or jaw).
Unusual bleeding or bruising.
Unusual tiredness or weakness.

If you notice these less serious side effects, talk with your doctor:
- Anxiety, restlessness, or nervousness.
- Headache or flu symptoms.
- Nausea, vomiting, upset stomach.
- Redness, pain, swelling, itching, blistering, or rash where the shot was given.
- Weight gain or loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy

A) Aripiprazole (oral formulation) is indicated for the treatment of schizophrenia, and for the treatment of acute manic and mixed episodes associated with bipolar disorder. The intramuscular formulation is indicated for the treatment of agitation associated with schizophrenia or bipolar disorder, manic or mixed (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION
1) Aripiprazole is an atypical antipsychotic agent (quinolinone derivative). It exhibits relatively high affinity for dopamine D2 and D3 receptors and serotonin 5-HT1A and 5-HT2A receptors (Prod Info Abilify(TM), 2002b; Lawler et al, 1999; Inoue & Nakata, 2001). The efficacy of the drug in schizophrenia appears related to partial agonist activity at D2 and 5-HT1A receptors (Lawler et al, 1999; Prod Info Abilify(TM), 2002b; Inoue & Nakata, 2001; Matsubayashi et al, 1999), and antagonist activity at 5-HT2A receptors has also been speculated (Prod Info Abilify(TM), 2002b).
2) However, other actions may be involved. In vitro data have indicated D2- agonist activity of aripiprazole at presynaptic autoreceptors, with antagonist activity at postsynaptic D2 receptors (regulating inhibition of cAMP synthesis) (Inoue et al, 2001; Inoue & Nakata, 2001; Matsubayashi et al, 1999; Lawler et al, 1999; Prioleau et al, 1998). These dual effects are seen at the same dose level (concentration) (Lawler et al, 1999), and are unlike those of conventional antipsychotic drugs (typical and atypical). Preclinical and clinical data suggest that these actions minimize extrapyramidal and endocrine (eg, prolactin increases) side effects (Inoue et al, 2001; Inoue & Nakata, 2001; Lawler et al, 1999).
3) Electrophysiological studies in animals suggest that aripiprazole acts as a dopamine-D2 agonist on dopaminergic neurons of the ventral tegmental area, and as a dopamine-D2 (and possibly D3) antagonist on striatal neurons and nucleus accumbens neurons (Matsubayashi et al, 1999).
4) In a small magnetoencephalographic study involving schizophrenic patients (n=5), treatment with aripiprazole for two months was associated with a decrease (normalizing effect) of abnormal delta and theta activity, loosely correlating with decreases in Positive and Negative Syndrome Scale (PANSS) scores (Canive et al, 1998). The authors suggest evaluation of delta activity (near-normalization) as a predictor of response to aripiprazole. However, additional data accumulation in a larger number of patients is needed.

B) REVIEW ARTICLES
1) Pharmacologic basis for using partial agonists in schizophrenia (Inoue & Nakata, 2001).

4.5 Therapeutic Uses

Asperger's disorder
Bipolar disorder, acute, acute manic or mixed episodes
Bipolar disorder - Psychomotor agitation
Psychomotor agitation - Schizophrenia
Schizophrenia

4.5.A Asperger's disorder

1) Overview
- FDA Approval: Adult, no; Pediatric, no
- Efficacy: Adult, Evidence is inconclusive
- Recommendation: Adult, Class IIb
- Strength of Evidence: Adult, Category C

2) Summary:
Improved symptoms of Asperger disorder in an adult patient

3) Adult:
   a) Aripiprazole treatment improved symptoms of anxiety, obsessive compulsion, hyperactivity, impaired judgment and social isolation in a male patient with lifelong Asperger disorder. The 34-year-old man had failed numerous medication trials over a 20-year period with very little alleviation of symptoms before aripiprazole therapy was introduced at 10 milligrams daily. Following two months of aripiprazole treatment, the patient presented as calm, patient, and attentive. He had become more relaxed cooperative and aware of himself. During an unplanned temporary discontinuation of aripiprazole, the patient's mood and behavior quickly deteriorated and then rapidly improved within days of re-initiating the medication. The patient continued to experience occasional obsessive-compulsive symptoms and depressed mood, but was well maintained at a daily 10 milligram dose. Controlled studies are needed to confirm these results and establish efficacy (Staller, 2003).

4.5.B Bipolar disorder, acute, acute manic or mixed episodes

FDA Labeled Indication

1) Overview
   - FDA Approval: Adult, yes; Pediatric, no
   - Efficacy: Adult, Evidence favors efficacy
   - Recommendation: Adult, Class IIb
   - Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Aripiprazole is indicated for the treatment of acute manic and mixed episodes associated with bipolar disorder (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006)

3) Adult:
   a) Aripiprazole was more effective than placebo in the treatment of acute manic or mixed episodes in patients with bipolar disorder. In a multicenter, randomized, double-blind, placebo-controlled study, patients (n=262) with bipolar disorder, mixed or manic episode, and a Young Mania Rating Scale (Y-MRS) score of at least 20 received aripiprazole 30 milligrams (mg)/day (reduced to 15 mg/day if needed; mean dose, 27.9 mg/day) or placebo for 3 weeks. Patients were hospitalized for at least the first 2 weeks of treatment. Response was defined as a reduction in the Y-MRS total score by at least 50%. From baseline to endpoint, total Y-MRS scores of aripiprazole-treated patients were significantly more improved as compared with patients who received placebo (mean, -8.2 vs -3.4, respectively; p=0.002). This significant difference was present from day 4 to endpoint. The response rate was also significantly higher in aripiprazole-treated patients as compared with placebo at all time points from day 4 (14% vs 5%, respectively; p less than 0.02) to endpoint (40% vs 19%, respectively; p less than or equal to 0.005). Adverse events were similar in both groups, however, nausea, dyspepsia, constipation, somnolence, vomiting, akathisia, and accidental injury occurred more than twice as often in the aripiprazole group as compared with placebo (Keck et al, 2003).

4.5.C Bipolar disorder - Psychomotor agitation

FDA Labeled Indication

1) Overview
   - FDA Approval: Adult, yes (injectable only); Pediatric, no
   - Efficacy: Adult, Effective
   - Recommendation: Adult, Class IIa
   - Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Aripiprazole intramuscular is approved for the treatment of agitation associated with schizophrenia and bipolar disorder, manic or mixed (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006)

In one short-term (24-hour), placebo-controlled trial, intramuscular aripiprazole was statistically superior to placebo in improving symptoms of agitation in patients with Bipolar I Disorder (manic or mixed; using the Positive and Negative Syndrome Scale [PANSS] Excited Component scores and the Clinical Global Impression of Improvement [CGI-I] scale scores) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006)

In one short-term (24-hour), placebo-controlled trial (n=291), intramuscular aripiprazole (fixed doses of 9.75 milligrams (mg) and 15 mg evaluated) was statistically superior to placebo in improving symptoms of agitation in patients with Bipolar I Disorder (manic or mixed; using the Positive and Negative Syndrome Scale [PANSS] Excited Component scores and the Clinical Global Impression of Improvement [CGI-I] scale scores) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006)

3) Adult:
   a) In one short-term (24-hour), placebo-controlled trial (n=291), intramuscular aripiprazole (fixed doses of 9.75 milligrams (mg) and 15 mg evaluated) was statistically superior to placebo in improving symptoms of agitation in patients with Bipolar I Disorder (manic or mixed; using the Positive and Negative Syndrome Scale [PANSS] Excited Component scores and the Clinical Global Impression of Improvement [CGI-I] scale scores). The trial included a single active comparator treatment arm of lorazepam injection. Agitated patients predominantly meeting DSM-IV criteria for Bipolar I Disorder (manic or mixed) received up to 3 injections during the 24-treatment period, with the second injection administered after the initial 2-hour period, when the primary efficacy measure was evaluated. All enrolled patients were judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication. Additionally, all patients exhibited a level of agitation that met or exceeded a threshold score of 14 or greater on the five items comprising the PANSS Excited Component (e.g.; poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least 2 individual item scores of 4 or greater using a 1 to 7 scoring system (1=absent, 4=moderate, 7=extreme). In this study, the baseline PANSS Excited Component score ranged from 15 to 24 (out of a maximum score of 35) with the mean baseline score of 19; this suggested mainly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The
primary efficacy measure in this trial was the change in the PANSS Excited Component from baseline to 2 hours post-injection. The CGI-I scale was a key secondary measure. After the initial 2-hour period, both doses (9.75 mg and 15 mg) were statistically superior to placebo in the PANSS Excited Component and on the CGI-I scale. There was no additional benefit demonstrated for the 15 mg dose when compared to the 9.75 mg dose (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

4.5.D Psychomotor agitation - Schizophrenia

FDA Labeled Indication
1) Overview
FDA Approval: Adult, yes (injectable only); Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
Aripiprazole intramuscular is approved for the treatment of agitation associated with schizophrenia and bipolar disorder, manic or mixed (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

A double-blind, placebo-controlled study demonstrated that intramuscular aripiprazole was noninferior to intramuscular haloperidol and superior to placebo in voluntarily hospitalized agitated patients with schizophrenia or schizoaffective disorder (Andrezina et al, 2006).

In two short-term (24-hour), placebo-controlled trials, intramuscular aripiprazole was statistically superior to placebo in improving symptoms of agitation in patients with schizophrenia (using the Positive and Negative Syndrome Scale [PANSS] Excited Component scores and the Clinical Global Impression of Improvement [CGI-I] scale scores) (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

3) Adult:
a) A double-blind, placebo-controlled study demonstrated that intramuscular aripiprazole was noninferior to intramuscular haloperidol and superior to placebo in voluntarily hospitalized, agitated patients with schizophrenia or schizoaffective disorder as measured by a change from baseline in PEC (5 excited components from the Positive and Negative Syndrome Scale [PANSS]) to 2 hours after the first injection. The PEC rated hostility, lack of cooperation, excitement, poor impulse control, and tension on a scale of 1 (absent) to 7 (extreme). Patients were randomized to receive either aripiprazole 9.75 mg intramuscularly (IM) (n=175), haloperidol 6.5 mg IM (n=185), or placebo (n=88). The noninferiority margin of mean change from baseline in PEC score was 2.5. Patients could receive up to three IM injections spaced at least 2 hours apart. Analysis of the primary efficacy endpoint demonstrated an improvement in PEC score at 2 hours from baseline of -7.27 aripiprazole group, -7.75 haloperidol group, and -4.78 placebo (p < 0.001). At 2 hours after the first injection the percentage of patients achieving a clinical response (defined as a reduction in PEC score from baseline of 40% or greater) was achieved by 55% aripiprazole group, 58% haloperidol group, and 36% in the placebo group (p < 0.005). Patients requiring a second injection occurred in 41% aripiprazole patients (n=70), 34% haloperidol patients (n=62), and 57% in placebo (n=50), with reductions in PEC 2 hours following the second dose of -5.92, -6.73 and -2.16 (p < 0.001 vs placebo), respectively. The most frequently reported adverse effects in the aripiprazole group (n=175) was headache (7.4%), dizziness (6.3%), nausea (5.7%) and insomnia (5.7%), and in the haloperidol group (n=183) was insomnia (12%), headache (8.2%), and extrapyramidal disorder (5.5%) (Andrezina et al, 2006).

b) In two short-term (24-hour), placebo-controlled trials, intramuscular aripiprazole was statistically superior to placebo in improving symptoms of agitation in patients with schizophrenia (using the Positive and Negative Syndrome Scale [PANSS] Excited Component scores and the Clinical Global Impression of Improvement [CGI-I] scale scores). Both trials included a single active comparator treatment arm of haloperidol injection. Agitated patients predominantly meeting DSM-IV criteria for schizophrenia received up to 3 injections during the 24-treatment period, with the second injection administered after the initial 2-hour period, when the primary efficacy measure was evaluated. All enrolled patients were judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication. Additionally, all patients exhibited a level of agitation that met or exceeded a threshold score of 14 or greater on the five items comprising the PANSS Excited Component (eg; poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least 2 individual item scores of 4 or greater using a 1 to 7 scoring system (1=absent, 4=moderate, 7=extreme). In both studies, the baseline PANSS Excited Component score ranged from 15 to 24 (out of a maximum score of 35) with the mean baseline score of 19; this suggested mainly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure in both trials was the change in the PANSS Excited Component from baseline to 2 hours post-injection. The CGI-I scale was a key secondary measure. In the first study (n=350), four fixed aripiprazole injection doses of 1 milligram (mg), 5.25 mg, 9.75 mg and 15 mg were evaluated. After the initial 2-hour period, the 5.25 mg, 9.75 mg, and 15 mg doses were statistically superior to placebo in the PANSS Excited Component and on the CGI-I scale. In the second study (n=445), one fixed aripiprazole injection dose of 9.75 mg was evaluated. After the initial 2-hour period, aripiprazole injection was statistically superior to placebo in the PANSS Excited Component on the CGI-I scale (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, oral solution, IM injection, 2006).

4.5.E Schizophrenia

FDA Labeled Indication
1) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
2) Summary:
Aripiprazole is indicated for the treatment of schizophrenia (Prod Info ABILIFY(R) oral tablets, orally-disintegrating tablets, solution, 2006)
Aripiprazole has been more effective than placebo in treating patients with acutely relapsed schizophrenia or schizoaffective disorder; it may improve cognitive function in some patients (Petrie et al, 1998a; Saha et al, 1999b)

Lengthened time to relapse in patients with schizophrenia (Anon, 2003)

3) Adult:

a) SUMMARY

1) Relatively large double-blind, placebo-controlled studies (unpublished) have indicated the efficacy of oral aripiprazole 10 to 30 milligrams (mg) daily in patients with acute relapse of schizophrenia or schizoaffective disorder (Petrie et al, 1998a; Kane et al, 2000b; Saha et al, 1999b; Anon, 2000c). The optimal dose appears to be 10 or 15 mg once daily; additional clinical benefit has not usually been observed with higher doses (Prod Info ABILIFY(R) oral tablets, disintegrating tablets, solution, 2006). These studies included significant improvement relative to placebo on Positive and Negative Syndrome Scale (PANSS)-total, PANSS-positive, PANSS-negative, Clinical Global Improvement (CGI)-severity, and Brief Psychiatric Rating Scale (BPRS) scores. The drug demonstrated a low propensity for extrapyramidal symptoms. All studies have been of short duration (4 to 6 weeks); an extended open treatment phase was instituted in one study (Petrie et al, 1998a), although results were not provided.

b) Aripiprazole therapy was effective in the prevention of relapse in patients with chronic, stable schizophrenia. In a multicenter, randomized, double-blind, placebo-controlled study, patients (n=310) with at least a 2-year history of schizophrenia and stable symptoms during the previous 3 months received oral aripiprazole (15 milligrams daily) or placebo for 26 weeks. Time to relapse after randomization was significantly longer in aripiprazole-treated patients as compared with patients who received placebo (p less than 0.001). Additionally, a higher number of patients in the placebo group relapsed as compared with those in the aripiprazole group (57% vs 33.8%, respectively). The relative risk for relapse with aripiprazole treatment versus placebo was 0.59 (95% CI=0.45 to 0.75; p less than 0.001). Mean changes from baseline to endpoint were also significantly greater with aripiprazole therapy as compared with placebo for the Positive and Negative Syndrome Scale (PANSS) total score, PANSS positive subscale score, PANSS derived Brief Psychiatric Rating Scale (BPRS) core score, Clinical Global Impression-Improvement (CGI-I) score (p less than or equal to 0.01, all values), and CGI-Severity score (p less than or equal to 0.05). Insomnia, tremor, akathisia, vomiting, and nausea were the most frequently reported adverse events with aripiprazole therapy (Pigott et al, 2003)(Anon, 2003).

c) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (n=414), aripiprazole 15 or 30 mg daily and haloperidol 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes in PANSS-total and BPRS-total scores; based on responder analysis (a 30% reduction in PANSS-total scores from baseline at last visit), each dose of aripiprazole was significantly more effective than placebo, whereas haloperidol was not. There was evidence of better tolerability with aripiprazole compared to haloperidol (eg, benzotropine requirements for extrapyramidal effects, prolactin increases, weight increase). Extrapyramidal symptoms were reportedly similar with aripiprazole and placebo, and fewer patients receiving aripiprazole discontinued treatment due to adverse events compared to haloperidol and placebo (Kane et al, 2000b). However, this study did not report statistical comparisons of aripiprazole and haloperidol for any parameter (efficacy versus baseline or adverse effects); responder-analysis data revealed only a small difference between the two drugs. Overall, this study does not provide evidence that aripiprazole is significantly more efficacious than haloperidol.

d) Some improvement in neurocognitive function (eg, verbal learning, executive functioning, vigilance) was reported during aripiprazole therapy (30 mg daily) in a randomized study (n=256); the drug tended to be superior to olanzapine (Kern et al, 2001a). However, a placebo group was lacking.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Chlorpromazine
Haloperidol
Olanzapine

4.6.A Chlorpromazine

4.6.A.1 Schizophrenia

a) Based upon comparisons of minimum effective dosages identified in placebo-controlled, fixed-dose and fixed-dose-ranging drug development trials, the minimum effective dose of aripiprazole was 15 milligrams/day (equivalent to chlorpromazine 200 milligrams/day) (Woods SW, 2003).

4.6.B Haloperidol

4.6.B.1 Schizophrenia

a) SUMMARY: Aripiprazole (up to 30 mg daily) and haloperidol (up to 20 mg daily) appear similarly effective in patients with acutely relapsed schizophrenia or schizoaffective disorder; adverse effects may be less with aripiprazole.

b) Haloperidol 5 to 20 mg daily, but not aripiprazole (5 to 30 mg daily), was superior to placebo with respect to improvement in BPRS scores in a 4-week study involving acutely relapsed inpatients with DSM-III/IV schizophrenia (n=103). Both haloperidol and aripiprazole were more effective than placebo in responder analysis based on CGI-severity scores (Prod Info Abilify(TM), 2002).

c) In a placebo-controlled, phase III study involving relapsed schizophrenic or schizoaffective patients (n=414), aripiprazole 15 or 30 mg daily and haloperidol 10 mg daily (fixed doses) were each statistically superior to placebo with regard to changes in PANSS-total and BPRS-total scores; based on responder analysis (a 30% reduction in PANSS-total scores from baseline at last visit), each dose of aripiprazole was significantly more effective than placebo, whereas haloperidol was not. There was evidence of better tolerability with aripiprazole compared to haloperidol (eg, benzotropine requirements for extrapyramidal effects, prolactin increases, weight increase). Extrapyramidal symptoms were reportedly similar with aripiprazole and placebo, and fewer patients receiving aripiprazole discontinued treatment due to adverse events compared to haloperidol and placebo (Kane et al, 2000). However, this study did not report statistical comparisons of aripiprazole and haloperidol for any parameter (efficacy versus baseline or adverse effects); responder-analysis data revealed only a small difference between the two drugs. Overall, this study does not provide evidence that aripiprazole is significantly more efficacious than haloperidol.

d) Results of phase II studies also suggested fewer adverse effects with aripiprazole compared to haloperidol (Saha et al, 1999; Anon, 2000). In these studies, lower changes from
baseline in Simpson-Angus Scale scores (parkinsonian symptoms) and less requirement for benztropine were observed with all doses of aripiprazole (2, 10, or 30 mg daily) than with haloperidol 10 mg daily; prolactin levels were not increased by aripiprazole, compared to significant increases with haloperidol, and significantly less weight gain was evident in the aripiprazole groups (all doses). Comparative efficacy data were not presented.

4.6.C Olanzapine

4.6.C.1 Schizophrenia

a) A trend toward greater improvement in some areas of neurocognitive function (e.g., verbal learning, working memory) was reported for aripiprazole 30 mg daily compared to olanzapine 15 mg daily in a randomized study (n=256) (Kern et al, 2001). However, a placebo group was lacking, and details of this study are unavailable (unpublished).

6.0 References