

Rx only**ABILIFY[®] (aripiprazole) Tablets****ABILIFY[®] DISCMELT[™] (aripiprazole) Orally****Disintegrating Tablets****ABILIFY[®] (aripiprazole) Oral Solution****ABILIFY[®] (aripiprazole) Injection FOR INTRAMUSCULAR
USE ONLY****WARNING****Increased Mortality in Elderly Patients with Dementia-Related
Psychosis**

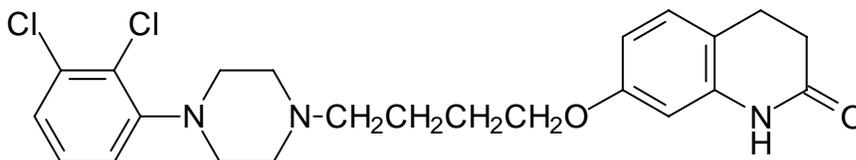
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to 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 (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis.

DESCRIPTION

Aripiprazole is a psychotropic drug that is available as ABILIFY[®] (aripiprazole) tablets, ABILIFY[®] DISCMELT[™] (aripiprazole) orally disintegrating tablets, a solution for oral administration, and a solution for intramuscular injection. Aripiprazole is 7-[4-[4-(2,3-

26 dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl. The empirical formula is
27 $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.39.

28 The chemical structure is:



29

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

34 ABILIFY DISCMELT orally disintegrating tablets are available in 10-mg and 15-
35 mg strengths. Inactive ingredients include acesulfame potassium, aspartame, calcium
36 silicate, croscarmellose sodium, crospovidone, crème de vanilla (natural and artificial
37 flavors), magnesium stearate, microcrystalline cellulose, silicon dioxide, tartaric acid, and
38 xylitol. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum
39 Lake.

40 ABILIFY is also available as a 1 mg/mL oral solution. The inactive ingredients
41 for this solution include disodium edetate, fructose, glycerin, dl-lactic acid,
42 methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose, and
43 purified water. The oral solution is flavored with natural orange cream and other natural
44 flavors.

45 ABILIFY Injection is available in single-dose vials as a ready-to-use, 9.75 mg/1.3
46 mL (7.5 mg/mL) clear, colorless, sterile, aqueous solution for intramuscular use only.
47 Inactive ingredients for this solution include 150 mg/mL of sulfobutylether β -
48 cyclodextrin (SBECD), tartaric acid, sodium hydroxide, and water for injection.

49 CLINICAL PHARMACOLOGY

50 Pharmacodynamics

51 Aripiprazole exhibits high affinity for dopamine D₂ and D₃, serotonin 5-HT_{1A} and 5-
52 HT_{2A} receptors (K_i values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity
53 for dopamine D₄, serotonin 5-HT_{2C} and 5-HT₇, alpha₁-adrenergic and histamine H₁
54 receptors (K_i values of 44, 15, 39, 57, and 61 nM, respectively), and moderate affinity for
55 the serotonin reuptake site (K_i=98 nM). Aripiprazole has no appreciable affinity for
56 cholinergic muscarinic receptors (IC₅₀>1000 nM). Aripiprazole functions as a partial
57 agonist at the dopamine D₂ and the serotonin 5-HT_{1A} receptors, and as an antagonist at
58 serotonin 5-HT_{2A} receptor.

59 The mechanism of action of aripiprazole, as with other drugs having efficacy in
60 schizophrenia, bipolar disorder, and agitation associated with schizophrenia or bipolar
61 disorder, is unknown. However, it has been proposed that the efficacy of aripiprazole is
62 mediated through a combination of partial agonist activity at D₂ and 5-HT_{1A} receptors
63 and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D₂, 5-HT_{1A},
64 and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole, eg, the
65 orthostatic hypotension observed with aripiprazole may be explained by its antagonist
66 activity at adrenergic alpha₁ receptors.

67 **Pharmacokinetics**

68 ABILIFY activity is presumably primarily due to the parent drug, aripiprazole, and to a
69 lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to
70 have affinities for D₂ receptors similar to the parent drug and represents 40% of the
71 parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and
72 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state
73 concentrations are attained within 14 days of dosing for both active moieties.
74 Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady
75 state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of
76 aripiprazole is mainly through hepatic metabolism involving two P450 isozymes,
77 CYP2D6 and CYP3A4.

78 Pharmacokinetic studies showed that ABILIFY DISCMELT orally disintegrating
79 tablets are bioequivalent to ABILIFY tablets.

80 **ORAL ADMINISTRATION**

81 **Absorption**

82 **Tablet**

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

89 **Oral Solution**

90 Aripiprazole is well absorbed when administered orally as the solution. At equivalent
91 doses, the plasma concentrations of aripiprazole from the solution were higher than that
92 from the tablet formulation. In a relative bioavailability study comparing the
93 pharmacokinetics of 30 mg aripiprazole as the oral solution to 30 mg aripiprazole tablets
94 in healthy subjects, the solution to tablet ratios of geometric mean C_{max} and AUC values
95 were 122% and 114%, respectively (see **DOSAGE AND ADMINISTRATION**). The
96 single-dose pharmacokinetics of aripiprazole were linear and dose-proportional between
97 the doses of 5 to 30 mg.

98 **Distribution**

99 The steady-state volume of distribution of aripiprazole following intravenous
100 administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution.
101 At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99%
102 bound to serum proteins, primarily to albumin. In healthy human volunteers administered
103 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent D₂ receptor
104 occupancy indicating brain penetration of aripiprazole in humans.

105 **Metabolism and Elimination**

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

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

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

126 **INTRAMUSCULAR ADMINISTRATION**

127 In 2 pharmacokinetic studies of aripiprazole injection administered intramuscularly to
128 healthy subjects, the median times to the peak plasma concentrations were at 1 and 3
129 hours. A 5-mg intramuscular injection of aripiprazole had an absolute bioavailability of
130 100%. The geometric mean maximum concentration achieved after an intramuscular dose
131 was on average 19% higher than the C_{max} of the oral tablet. While the systemic exposure
132 over 24 hours was generally similar between aripiprazole injection given intramuscularly
133 and after oral tablet administration, the aripiprazole AUC in the first 2 hours after an
134 intramuscular injection was 90% greater than the AUC after the same dose as a tablet. In
135 stable patients with schizophrenia or schizoaffective disorder, the pharmacokinetics of

136 aripiprazole after intramuscular administration were linear over a dose range of 1 to 45
137 mg. Although the metabolism of aripiprazole injection was not systematically evaluated,
138 the intramuscular route of administration would not be expected to alter the metabolic
139 pathways.

140 **Special Populations**

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

145 **Hepatic Impairment**

146 In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver
147 cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to
148 healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased
149 20% in severe HI. None of these differences would require dose adjustment.

150 **Renal Impairment**

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

157 **Elderly**

158 In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of
159 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared
160 to younger adult subjects (18 to 64 years). There was no detectable age effect; however,
161 in the population pharmacokinetic analysis in schizophrenia patients. Also, the
162 pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar
163 to that observed in young, healthy subjects. No dosage adjustment is recommended for

164 elderly patients (see **Boxed WARNING, WARNINGS: Increased Mortality in Elderly**
165 **Patients with Dementia-Related Psychosis, and PRECAUTIONS: Geriatric Use**).

166 **Gender**

167 C_{max} and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to
168 40% higher in women than in men, and correspondingly, the apparent oral clearance of
169 aripiprazole is lower in women. These differences, however, are largely explained by
170 differences in body weight (25%) between men and women. No dosage adjustment is
171 recommended based on gender.

172 **Race**

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

177 **Smoking**

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

184 **Drug-Drug Interactions**

185 **Potential for Other Drugs to Affect ABILIFY**

186 Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8,
187 CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct
188 glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or
189 inducers of these enzymes, or other factors, like smoking, is unlikely.

190 Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents
191 that induce CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole
192 clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6
193 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause
194 increased blood levels.

195 **Potential for ABILIFY to Affect Other Drugs**

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

203 *Aripiprazole had no clinically important interactions with the following drugs:*

204 *Famotidine:* Coadministration of aripiprazole (given in a single dose of 15 mg)
205 with a 40-mg single dose of the H₂ antagonist famotidine, a potent gastric acid blocker,
206 decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by
207 37% and 21% the C_{max} of aripiprazole and dehydro-aripiprazole, respectively, and by
208 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of
209 aripiprazole is required when administered concomitantly with famotidine.

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

214 *Lithium:* A pharmacokinetic interaction of aripiprazole with lithium is unlikely
215 because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely
216 excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200-
217 1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically
218 significant changes in the pharmacokinetics of aripiprazole or its active metabolite,
219 dehydro-aripiprazole (C_{max} and AUC increased by less than 20%). No dosage
220 adjustment of aripiprazole is required when administered concomitantly with lithium.

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

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

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

237 *Lorazepam:* Coadministration of lorazepam injection (2 mg) and aripiprazole
238 injection (15 mg) to healthy subjects (N=40: 35 males and 5 females; ages 19-45 years
239 old) did not result in clinically important changes in the pharmacokinetics of either drug.
240 No dosage adjustment of aripiprazole is required when administered concomitantly with
241 lorazepam. However, the intensity of sedation was greater with the combination as
242 compared to that observed with aripiprazole alone and the orthostatic hypotension
243 observed was greater with the combination as compared to that observed with lorazepam
244 alone (see **PRECAUTIONS: General**).

245 **Clinical Studies**

246 **Schizophrenia**

247 The efficacy of ABILIFY in the treatment of schizophrenia was evaluated in four short-
248 term (4- and 6-week), placebo-controlled trials of acutely relapsed inpatients who
249 predominantly met DSM-III/IV criteria for schizophrenia. Three of the four trials were
250 able to distinguish aripiprazole from placebo, but one study, the smallest, did not. Three

251 of these studies also included an active control group consisting of either risperidone (one
252 trial) or haloperidol (two trials), but they were not designed to allow for a comparison of
253 ABILIFY and the active comparators.

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

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

271 In a 4-week trial (n=404) comparing two fixed doses of ABILIFY (20 or
272 30 mg/day) and risperidone (6 mg/day) to placebo, both doses of ABILIFY were superior
273 to placebo in the PANSS total score, PANSS positive subscale, PANSS negative
274 subscale, and CGI-severity score.

275 In a 6-week trial (n=420) comparing three fixed doses of ABILIFY (10, 15, or
276 20 mg/day) to placebo, all three doses of ABILIFY were superior to placebo in the
277 PANSS total score, PANSS positive subscale, and the PANSS negative subscale.

278 In a fourth study, a 4-week trial (n=103) comparing ABILIFY in a range of 5 to
279 30 mg/day or haloperidol 5 to 20 mg/day to placebo, haloperidol was superior to placebo,
280 in the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general
281 psychopathology traditionally used to evaluate the effects of drug treatment in psychosis,
282 and in a responder analysis based on the CGI-severity score, the primary outcomes for

283 that trial. ABILIFY was only significantly different compared to placebo in a responder
284 analysis based on the CGI-severity score.

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

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

291 A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV
292 criteria for schizophrenia who were, by history, symptomatically stable on other
293 antipsychotic medications for periods of 3 months or longer. These patients were
294 discontinued from their antipsychotic medications and randomized to ABILIFY 15 mg or
295 placebo for up to 26 weeks of observation for relapse. Relapse during the double-blind
296 phase was defined as CGI-Improvement score of ≥ 5 (minimally worse), scores ≥ 5
297 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or $\geq 20\%$
298 increase in the PANSS total score. Patients receiving ABILIFY 15 mg experienced a
299 significantly longer time to relapse over the subsequent 26 weeks compared to those
300 receiving placebo.

301 **Bipolar Disorder**

302 The efficacy of ABILIFY in the treatment of acute manic episodes was established in two
303 3-week, placebo-controlled trials in hospitalized patients who met the DSM-IV criteria
304 for Bipolar I Disorder with manic or mixed episodes (in one trial, 21% of placebo and
305 42% of ABILIFY-treated patients had data beyond two weeks). These trials included
306 patients with or without psychotic features and with or without a rapid-cycling course.

307 The primary instrument used for assessing manic symptoms was the Young
308 Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess
309 the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep,
310 elevated mood, speech, increased activity, sexual interest, language/thought disorder,
311 thought content, appearance, and insight) in a range from 0 (no manic features) to 60
312 (maximum score). A key secondary instrument included the Clinical Global Impression -
313 Bipolar (CGI-BP) scale.

314 In the two positive, 3-week, placebo-controlled trials (n=268; n=248) which
315 evaluated ABILIFY 15 or 30 mg/day, once daily (with a starting dose of 30 mg/day),
316 ABILIFY was superior to placebo in the reduction of Y-MRS total score and CGI-BP
317 Severity of Illness score (mania).

318 A trial was conducted in patients meeting DSM-IV criteria for Bipolar I Disorder
319 with a recent manic or mixed episode who had been stabilized on open-label ABILIFY
320 and who had maintained a clinical response for at least 6 weeks. The first phase of this
321 trial was an open-label stabilization period in which inpatients and outpatients were
322 clinically stabilized and then maintained on open-label ABILIFY (15 or 30 mg/day, with
323 a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one
324 outpatients were then randomized in a double-blind fashion, to either the same dose of
325 ABILIFY they were on at the end of the stabilization and maintenance period or placebo
326 and were then monitored for manic or depressive relapse. During the randomization
327 phase, ABILIFY was superior to placebo on time to the number of combined affective
328 relapses (manic plus depressive), the primary outcome measure for this study. The
329 majority of these relapses were due to manic rather than depressive symptoms. There is
330 insufficient data to know whether ABILIFY is effective in delaying the time to
331 occurrence of depression in patients with Bipolar I Disorder.

332 An examination of population subgroups did not reveal any clear evidence of
333 differential responsiveness on the basis of age and gender; however, there were
334 insufficient numbers of patients in each of the ethnic groups to adequately assess inter-
335 group differences.

336 **Agitation Associated with Schizophrenia or Bipolar Mania**

337 The efficacy of intramuscular aripiprazole for injection for the treatment of agitation was
338 established in three short-term (24 hour), placebo-controlled trials in agitated inpatients
339 from two diagnostic groups: schizophrenia and Bipolar I Disorder (manic or mixed
340 episodes, with or without psychotic features). Each of the trials included a single active
341 comparator treatment arm of either haloperidol injection (schizophrenia studies) or
342 lorazepam injection (bipolar mania study). Patients could receive up to three injections
343 during the 24-hour treatment periods; however, patients could not receive the second
344 injection until after the initial 2-hour period when the primary efficacy measure was
345 assessed. Patients enrolled in the trials needed to be: (1) judged by the clinical

346 investigators as clinically agitated and clinically appropriate candidates for treatment with
347 intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a
348 threshold score of ≥ 14 on the five items comprising the Positive and Negative Syndrome
349 Scale (PANSS) Excited Component (ie, poor impulse control, tension, hostility,
350 uncooperativeness and excitement items) with at least two individual item scores ≥ 4
351 using a 1-7 scoring system (1 = absent, 4 = moderate, 7 = extreme). In the studies, the
352 mean baseline PANSS Excited Component score was 19, with scores ranging from 15 to
353 34 (out of a maximum score of 35), thus suggesting predominantly moderate levels of
354 agitation with some patients experiencing mild or severe levels of agitation. The primary
355 efficacy measure used for assessing agitation signs and symptoms in these trials was the
356 change from baseline in the PANSS Excited Component at 2 hours post-injection. A key
357 secondary measure was the Clinical Global Impression of Improvement (CGI-I) scale.
358 The results of the trials follow:

359 (1) In a placebo-controlled trial in agitated inpatients predominantly
360 meeting DSM-IV criteria for schizophrenia (n=350), four fixed
361 aripiprazole injection doses of 1 mg, 5.25 mg, 9.75 mg, and 15 mg were
362 evaluated. At 2 hours post-injection, the 5.25 mg, 9.75 mg, and 15 mg
363 doses were statistically superior to placebo in the PANSS Excited
364 Component and on the CGI-I scale.

365 (2) In a second placebo-controlled trial in agitated inpatients
366 predominantly meeting DSM-IV criteria for schizophrenia (n=445), one
367 fixed aripiprazole injection dose of 9.75 mg was evaluated. At 2 hours
368 post-injection, aripiprazole for injection was statistically superior to
369 placebo in the PANSS Excited Component and on the CGI-I scale

370 (3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV
371 criteria for Bipolar I Disorder (manic or mixed) (n=291), two fixed
372 aripiprazole injection doses of 9.75 mg and 15 mg were evaluated. At 2
373 hours post-injection, both doses were statistically superior to placebo in
374 the PANSS Excited Component.

375 Examination of population subsets (age, race, and gender) did not reveal any
376 differential responsiveness on the basis of these subgroupings.

377 **INDICATIONS AND USAGE**

378 **Schizophrenia**

379 ABILIFY is indicated for the treatment of schizophrenia. The efficacy of ABILIFY in the
380 treatment of schizophrenia was established in short-term (4- and 6-week) controlled trials
381 of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

382 The efficacy of ABILIFY in maintaining stability in patients with schizophrenia
383 who had been symptomatically stable on other antipsychotic medications for periods of 3
384 months or longer, were discontinued from those other medications, and were then
385 administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26
386 weeks was demonstrated in a placebo-controlled trial (see **CLINICAL**
387 **PHARMACOLOGY: Clinical Studies**). The physician who elects to use ABILIFY for
388 extended periods should periodically re-evaluate the long-term usefulness of the drug for
389 the individual patient (see **DOSAGE AND ADMINISTRATION**).

390 **Bipolar Disorder**

391 ABILIFY is indicated for the treatment of acute manic and mixed episodes associated
392 with Bipolar Disorder.

393 The efficacy of ABILIFY was established in two placebo-controlled trials (3
394 week) of inpatients with DSM-IV criteria for Bipolar I Disorder who were experiencing
395 an acute manic or mixed episode with or without psychotic features (see **CLINICAL**
396 **PHARMACOLOGY: Clinical Studies**).

397 The efficacy of ABILIFY in maintaining efficacy in patients with Bipolar I
398 Disorder with a recent manic or mixed episode who had been stabilized and then
399 maintained for at least 6 weeks, was demonstrated in a double-blind, placebo-controlled
400 trial. Prior to entering the double-blind, randomization phase of this trial, patients were
401 clinically stabilized and maintained their stability for 6 consecutive weeks on ABILIFY.
402 Following this 6-week maintenance phase, patients were randomized to either placebo or
403 ABILIFY and monitored for relapse (see **CLINICAL PHARMACOLOGY: Clinical**
404 **Studies**). Physicians who elect to use ABILIFY for extended periods, that is, longer than

405 6 weeks, should periodically re-evaluate the long-term usefulness of the drug for the
406 individual patient (see **DOSAGE AND ADMINISTRATION**).

407 **Agitation Associated with Schizophrenia or Bipolar Mania**

408 ABILIFY Injection is indicated for the treatment of agitation associated with
409 schizophrenia or bipolar disorder, manic or mixed. "Psychomotor agitation" is defined in
410 DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients
411 experiencing agitation often manifest behaviors that interfere with their diagnosis and
412 care (eg, threatening behaviors, escalating or urgently distressing behavior, or self-
413 exhausting behavior), leading clinicians to the use of intramuscular antipsychotic
414 medications to achieve immediate control of the agitation.

415 The efficacy of ABILIFY Injection for the treatment of agitation associated with
416 schizophrenia or Bipolar I Disorder was established in three short-term (24 hour),
417 placebo-controlled trials in agitated inpatients with schizophrenia or Bipolar I Disorder
418 (manic or mixed episodes) (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

419 **CONTRAINDICATIONS**

420 ABILIFY is contraindicated in patients with a known hypersensitivity to the product.

421 **WARNINGS**

422 **Increased Mortality in Elderly Patients with Dementia-Related** 423 **Psychosis**

424 **Elderly patients with dementia-related psychosis treated with atypical antipsychotic**
425 **drugs are at an increased risk of death compared to placebo. ABILIFY**
426 **(aripiprazole) is not approved for the treatment of patients with dementia-related**
427 **psychosis (see Boxed WARNING).**

428 **Neuroleptic Malignant Syndrome (NMS)**

429 A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant
430 Syndrome (NMS) has been reported in association with administration of antipsychotic
431 drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole

432 treatment in the premarketing worldwide clinical database. Clinical manifestations of
433 NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic
434 instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac
435 dysrhythmia). Additional signs may include elevated creatine phosphokinase,
436 myoglobinuria (rhabdomyolysis), and acute renal failure.

437 The diagnostic evaluation of patients with this syndrome is complicated. In
438 arriving at a diagnosis, it is important to exclude cases where the clinical presentation
439 includes both serious medical illness (eg, pneumonia, systemic infection, etc) and
440 untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other
441 important considerations in the differential diagnosis include central anticholinergic
442 toxicity, heat stroke, drug fever, and primary central nervous system pathology.

443 The management of NMS should include: 1) immediate discontinuation of
444 antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive
445 symptomatic treatment and medical monitoring; and 3) treatment of any concomitant
446 serious medical problems for which specific treatments are available. There is no general
447 agreement about specific pharmacological treatment regimens for uncomplicated NMS.

448 If a patient requires antipsychotic drug treatment after recovery from NMS, the
449 potential reintroduction of drug therapy should be carefully considered. The patient
450 should be carefully monitored, since recurrences of NMS have been reported.

451 **Tardive Dyskinesia**

452 A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop
453 in patients treated with antipsychotic drugs. Although the prevalence of the syndrome
454 appears to be highest among the elderly, especially elderly women, it is impossible to rely
455 upon prevalence estimates to predict, at the inception of antipsychotic treatment, which
456 patients are likely to develop the syndrome. Whether antipsychotic drug products differ
457 in their potential to cause tardive dyskinesia is unknown.

458 The risk of developing tardive dyskinesia and the likelihood that it will become
459 irreversible are believed to increase as the duration of treatment and the total cumulative
460 dose of antipsychotic drugs administered to the patient increase. However, the syndrome
461 can develop, although much less commonly, after relatively brief treatment periods at low
462 doses.

463 There is no known treatment for established cases of tardive dyskinesia, although
464 the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.
465 Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs
466 and symptoms of the syndrome and, thereby, may possibly mask the underlying process.
467 The effect that symptomatic suppression has upon the long-term course of the syndrome
468 is unknown.

469 Given these considerations, ABILIFY should be prescribed in a manner that is
470 most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic
471 treatment should generally be reserved for patients who suffer from a chronic illness that
472 (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally
473 effective, but potentially less harmful treatments are not available or appropriate. In
474 patients who do require chronic treatment, the smallest dose and the shortest duration of
475 treatment producing a satisfactory clinical response should be sought. The need for
476 continued treatment should be reassessed periodically.

477 If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, drug
478 discontinuation should be considered. However, some patients may require treatment
479 with ABILIFY despite the presence of the syndrome.

480 **Cerebrovascular Adverse Events, Including Stroke, in Elderly** 481 **Patients with Dementia-Related Psychosis**

482 In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of
483 dementia-related psychosis, there was an increased incidence of cerebrovascular adverse
484 events (eg, stroke, transient ischemic attack), including fatalities, in aripiprazole-treated
485 patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a
486 statistically significant dose response relationship for cerebrovascular adverse events in
487 patients treated with aripiprazole. Aripiprazole is not approved for the treatment of
488 patients with dementia-related psychosis. (See also **Boxed WARNING, WARNINGS:**
489 **Increased Mortality in Elderly Patients with Dementia-Related Psychosis**, and
490 **PRECAUTIONS: Use in Patients with Concomitant Illness: Safety Experience in**
491 *Elderly Patients with Psychosis Associated with Alzheimer's Disease.*)

492 **Hyperglycemia and Diabetes Mellitus**

493 Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar
494 coma or death, has been reported in patients treated with atypical antipsychotics. There
495 have been few reports of hyperglycemia in patients treated with ABILIFY. Although
496 fewer patients have been treated with ABILIFY, it is not known if this more limited
497 experience is the sole reason for the paucity of such reports. Assessment of the
498 relationship between atypical antipsychotic use and glucose abnormalities is complicated
499 by the possibility of an increased background risk of diabetes mellitus in patients with
500 schizophrenia and the increasing incidence of diabetes mellitus in the general population.
501 Given these confounders, the relationship between atypical antipsychotic use and
502 hyperglycemia-related adverse events is not completely understood. However,
503 epidemiological studies which did not include ABILIFY suggest an increased risk of
504 treatment-emergent hyperglycemia-related adverse events in patients treated with the
505 atypical antipsychotics included in these studies. Because ABILIFY was not marketed at
506 the time these studies were performed, it is not known if ABILIFY is associated with this
507 increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients
508 treated with atypical antipsychotics are not available.

509 Patients with an established diagnosis of diabetes mellitus who are started on
510 atypical antipsychotics should be monitored regularly for worsening of glucose control.
511 Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes)
512 who are starting treatment with atypical antipsychotics should undergo fasting blood
513 glucose testing at the beginning of treatment and periodically during treatment. Any
514 patient treated with atypical antipsychotics should be monitored for symptoms of
515 hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who
516 develop symptoms of hyperglycemia during treatment with atypical antipsychotics
517 should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved
518 when the atypical antipsychotic was discontinued; however, some patients required
519 continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

520 **PRECAUTIONS**

521 **General**

522 **Orthostatic Hypotension**

523 Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α_1 -
524 adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated
525 events from five short-term, placebo-controlled trials in schizophrenia (n=926) on oral
526 ABILIFY included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic
527 lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole
528 0.6%). The incidence of orthostatic hypotension-associated events from short-term,
529 placebo-controlled trials in bipolar mania (n=597) on oral ABILIFY included: orthostatic
530 hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%,
531 aripiprazole 0.5%), and syncope (placebo 0.9%, aripiprazole 0.5%). The incidence of
532 orthostatic hypotension associated events from short-term, placebo-controlled trials in
533 agitation associated with schizophrenia or bipolar mania (n=501) on ABILIFY Injection
534 included: orthostatic hypotension (placebo 0%, aripiprazole 0.6%), postural dizziness
535 (placebo 0.5%, aripiprazole 0.2%), and syncope (placebo 0%, aripiprazole 0.4%).

536 The incidence of a significant orthostatic change in blood pressure (defined as a
537 decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to
538 standing position) for aripiprazole was not statistically different from placebo (in
539 schizophrenia: 14% among oral aripiprazole-treated patients and 12% among placebo-
540 treated patients in bipolar mania: 3% among oral aripiprazole-treated patients and 2%
541 among placebo-treated patients and in patients with agitation associated with
542 schizophrenia or bipolar mania: 4% among aripiprazole injection-treated patients and 4%
543 among placebo-treated patients).

544 Aripiprazole should be used with caution in patients with known cardiovascular
545 disease (history of myocardial infarction or ischemic heart disease, heart failure or
546 conduction abnormalities), cerebrovascular disease, or conditions which would
547 predispose patients to hypotension (dehydration, hypovolemia, and treatment with
548 antihypertensive medications).

549 If parenteral benzodiazepine therapy is deemed necessary in addition to
550 aripiprazole injection treatment, patients should be monitored for excessive sedation and
551 for orthostatic hypotension (see **CLINICAL PHARMACOLOGY: Drug-Drug**
552 **Interactions**).

553 Seizure

554 Seizures occurred in 0.1% (1/926) of oral aripiprazole-treated patients with schizophrenia
555 in short-term, placebo-controlled trials. In short-term, placebo-controlled clinical trials of
556 patients with bipolar mania, 0.3% (2/597) of oral aripiprazole-treated patients and 0.2%
557 (1/436) of placebo-treated patients experienced seizures. In short-term, placebo-
558 controlled clinical trials of patients with agitation associated with schizophrenia or
559 bipolar mania, 0.2% (1/501) of aripiprazole injection-treated patients and 0% (0/220) of
560 placebo-treated patients experienced seizures.

561 As with other antipsychotic drugs, aripiprazole should be used cautiously in
562 patients with a history of seizures or with conditions that lower the seizure threshold, eg,
563 Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent
564 in a population of 65 years or older.

565 Potential for Cognitive and Motor Impairment

566 In short-term, placebo-controlled trials of schizophrenia, somnolence was reported in
567 11% of patients on oral ABILIFY compared to 8% of patients on placebo; somnolence
568 led to discontinuation in 0.1% (1/926) of patients with schizophrenia on oral ABILIFY in
569 short-term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar
570 mania, somnolence was reported in 14% of patients on oral ABILIFY compared to 7% of
571 patients on placebo, but did not lead to discontinuation of any patients with bipolar
572 mania. In short-term, placebo-controlled trials of patients with agitation associated with
573 schizophrenia or bipolar mania, somnolence (including sedation) was reported in 9% of
574 patients on ABILIFY Injection compared to 6% of patients on placebo. Somnolence
575 (including sedation) did not lead to discontinuation of any patients with agitation
576 associated with schizophrenia or bipolar mania.

577 Despite the relatively modest increased incidence of somnolence compared to
578 placebo, ABILIFY, like other antipsychotics, may have the potential to impair judgment,
579 thinking, or motor skills. Patients should be cautioned about operating hazardous
580 machinery, including automobiles, until they are reasonably certain that therapy with
581 ABILIFY does not affect them adversely.

582 Body Temperature Regulation

583 Disruption of the body's ability to reduce core body temperature has been attributed to
584 antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for
585 patients who will be experiencing conditions which may contribute to an elevation in
586 core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving
587 concomitant medication with anticholinergic activity, or being subject to dehydration.

588 **Dysphagia**

589 Esophageal dysmotility and aspiration have been associated with antipsychotic drug use.
590 Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients,
591 in particular those with advanced Alzheimer's dementia. Aripiprazole and other
592 antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia
593 (see **PRECAUTIONS: Use in Patients with Concomitant Illness**).

594 **Suicide**

595 The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder,
596 and close supervision of high-risk patients should accompany drug therapy. Prescriptions
597 for ABILIFY should be written for the smallest quantity consistent with good patient
598 management in order to reduce the risk of overdose.

599 **Use in Patients with Concomitant Illness**

600 Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses
601 (see **CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment** and
602 *Hepatic Impairment*) is limited.

603 ABILIFY has not been evaluated or used to any appreciable extent in patients
604 with a recent history of myocardial infarction or unstable heart disease. Patients with
605 these diagnoses were excluded from premarketing clinical studies.

606 *Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's*
607 *Disease:* In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients
608 with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range:
609 56-99 years), the treatment-emergent adverse events that were reported at an incidence of
610 $\geq 3\%$ and aripiprazole incidence at least twice that for placebo were asthenia (placebo 3%,
611 aripiprazole 8%), somnolence (placebo 3%, aripiprazole 9%), urinary incontinence

612 (placebo 1%, aripiprazole 5%), excessive salivation (placebo 0%, aripiprazole 4%), and
613 lightheadedness (placebo 1%, aripiprazole 4%).

614 The safety and efficacy of ABILIFY in the treatment of patients with psychosis
615 associated with dementia have not been established. If the prescriber elects to treat such
616 patients with ABILIFY, vigilance should be exercised, particularly for the emergence of
617 difficulty swallowing or excessive somnolence, which could predispose to accidental
618 injury or aspiration. (See also **Boxed WARNING, WARNINGS: Increased Mortality
619 in Elderly Patients with Dementia-Related Psychosis, and Cerebrovascular Adverse
620 Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis.**)

621 **Information for Patients**

622 Physicians are advised to discuss the following issues with patients for whom they
623 prescribe ABILIFY:

624 **Interference with Cognitive and Motor Performance**

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

629 **Pregnancy**

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

632 **Nursing**

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

634 **Concomitant Medication**

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

637 **Alcohol**

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

639 **Heat Exposure and Dehydration**

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

642 **Sugar Content**

643 Patients should be advised that each mL of ABILIFY oral solution contains 400 mg of
644 sucrose and 200 mg of fructose.

645 **Phenylketonurics**

646 Phenylalanine is a component of aspartame. Each ABILIFY DISCMELT orally
647 disintegrating tablet contains the following amounts: 10 mg - 1.12 mg phenylalanine and
648 15 mg - 1.68 mg phenylalanine.

649 **Drug-Drug Interactions**

650 Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is
651 taken in combination with other centrally acting drugs and alcohol. Due to its α_1 -
652 adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of
653 certain antihypertensive agents.

654 **Potential for Other Drugs to Affect ABILIFY**

655 Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8,
656 CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct
657 glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or
658 inducers of these enzymes, or other factors, like smoking, is unlikely.

659 Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents
660 that induce CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole
661 clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6
662 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause
663 increased blood levels.

664 *Ketoconazole:* Coadministration of ketoconazole (200 mg/day for 14 days) with a
665 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active
666 metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose
667 (400 mg/day) has not been studied. When concomitant administration of ketoconazole
668 with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal
669 dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have
670 similar effects and need similar dose reductions; weaker inhibitors (erythromycin,
671 grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from
672 the combination therapy, aripiprazole dose should then be increased.

673 *Quinidine:* Coadministration of a 10-mg single dose of aripiprazole with
674 quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of
675 aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-
676 aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose
677 when concomitant administration of quinidine with aripiprazole occurs. Other significant
678 inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have
679 similar effects and, therefore, should be accompanied by similar dose reductions. When
680 the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose
681 should then be increased.

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

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

692 **Potential for ABILIFY to Affect Other Drugs**

693 Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with
694 drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day

695 doses of aripiprazole had no significant effect on metabolism by CYP2D6
696 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and
697 CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-
698 aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*
699 (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**).

700 *Alcohol:* There was no significant difference between aripiprazole coadministered
701 with ethanol and placebo coadministered with ethanol on performance of gross motor
702 skills or stimulus response in healthy subjects. As with most psychoactive medications,
703 patients should be advised to avoid alcohol while taking ABILIFY.

704 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

705 **Carcinogenesis**

706 Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley
707 (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3,
708 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and
709 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2 ,
710 respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and
711 60 mg/kg/day (3 to 19 times the MRHD based on mg/m^2). Aripiprazole did not induce
712 tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas
713 and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary
714 doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC
715 and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of
716 mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1
717 times human exposure at MRHD based on AUC and 3 times the MRHD based on
718 mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical
719 adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human
720 exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2).

721 Proliferative changes in the pituitary and mammary gland of rodents have been
722 observed following chronic administration of other antipsychotic agents and are
723 considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole
724 carcinogenicity studies. However, increases in serum prolactin levels were observed in

725 female mice in a 13-week dietary study at the doses associated with mammary gland and
726 pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week
727 dietary studies at the dose associated with mammary gland tumors. The relevance for
728 human risk of the findings of prolactin-mediated endocrine tumors in rodents is
729 unknown.

730 **Mutagenesis**

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

741 **Impairment of Fertility**

742 Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times
743 the maximum recommended human dose [MRHD] on a mg/m² basis) of aripiprazole
744 from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and
745 increased corpora lutea were seen at all doses, but no impairment of fertility was seen.
746 Increased pre-implantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight
747 was seen at 20 mg/kg.

748 Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19
749 times the MRHD on a mg/m² basis) of aripiprazole from 9 weeks prior to mating through
750 mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy
751 was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

752 **Pregnancy**

753 **Pregnancy Category C**

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

756 Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and
757 10 times the maximum recommended human dose [MRHD] on a mg/m² basis) of
758 aripiprazole during the period of organogenesis. Gestation was slightly prolonged at
759 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by
760 decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal
761 ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup
762 survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and
763 increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at
764 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence
765 of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally,
766 delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive
767 performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and
768 increased post-implantation loss, likely mediated through effects on female offspring)
769 was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg, however, there was
770 no evidence to suggest that these developmental effects were secondary to maternal
771 toxicity.

772 In pregnant rats receiving aripiprazole injection intravenously (3, 9, and 27
773 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed
774 skeletal ossification were seen at the highest dose, which also caused some maternal
775 toxicity.

776 Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3,
777 and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the
778 MRHD based on mg/m²) of aripiprazole during the period of organogenesis. Decreased
779 maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment
780 caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg),
781 increased incidence of a skeletal abnormality (fused sternebrae at 30 and 100 mg/kg) and
782 minor skeletal variations (100 mg/kg).

783 In pregnant rabbits receiving aripiprazole injection intravenously (3, 10, and 30
784 mg/kg/day) during the period of organogenesis, the highest dose, which caused
785 pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal

786 abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-
787 effect dose was 10 mg/kg, which produced 15 times the human exposure at the MRHD
788 based on AUC, and is 6 times the MRHD based on mg/m^2 .

789 In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day
790 (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole perinatally and
791 postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity
792 and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and
793 decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

794 In rats receiving aripiprazole injection intravenously (3, 8, and 20 mg/kg/day)
795 from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8
796 and 20 mg/kg, and decreases in early postnatal pup weights and survival were seen at 20
797 mg/kg. These doses produced some maternal toxicity. There were no effects on postnatal
798 behavioral and reproductive development.

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

803 **Labor and Delivery**

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

805 **Nursing Mothers**

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

809 **Pediatric Use**

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

811

812 **Geriatric Use**

813 Of the 7951 patients treated with oral aripiprazole in premarketing clinical trials, 991
814 (12%) were ≥ 65 years old and 789 (10%) were ≥ 75 years old. The majority (88%) of the
815 991 patients were diagnosed with dementia of the Alzheimer's type.

816 Placebo-controlled studies of oral aripiprazole in schizophrenia or bipolar mania
817 did not include sufficient numbers of subjects aged 65 and over to determine whether
818 they respond differently from younger subjects. There was no effect of age on the
819 pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was
820 decreased by 20% in elderly subjects (≥ 65 years) compared to younger adult subjects (18
821 to 64 years), but there was no detectable effect of age in the population pharmacokinetic
822 analysis in schizophrenia patients.

823 Of the 749 patients treated with aripiprazole injection in clinical trials, 99 (13%)
824 were ≥ 65 years old and 78 (10%) were ≥ 75 years old. Placebo-controlled studies of
825 aripiprazole injection in patients with agitation associated with schizophrenia or bipolar
826 mania did not include sufficient numbers of subjects aged 65 and over to determine
827 whether they respond differently from younger subjects.

828 Studies of elderly patients with psychosis associated with Alzheimer's disease
829 have suggested that there may be a different tolerability profile in this population
830 compared to younger patients with schizophrenia (see **Boxed WARNING**,
831 **WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related**
832 **Psychosis; Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients**
833 **with Dementia-Related Psychosis**; and **PRECAUTIONS: Use in Patients with**
834 *Concomitant Illness*). The safety and efficacy of ABILIFY in the treatment of patients
835 with psychosis associated with Alzheimer's disease has not been established. If the
836 prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

837 **ADVERSE REACTIONS**

838 Aripiprazole has been evaluated for safety in 7951 patients who participated in multiple-
839 dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the
840 Alzheimer's type, and who had approximately 5235 patient-years of exposure to oral
841 aripiprazole and 749 patients with exposure to aripiprazole injection. A total of 2280

842 patients were treated with oral aripiprazole for at least 180 days and 1558 patients treated
843 with oral aripiprazole had at least 1 year of exposure.

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

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

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

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

870 **ORAL ADMINISTRATION**

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

873 The following findings are based on a pool of five placebo-controlled trials (four 4-week
874 and one 6-week) in which oral aripiprazole was administered in doses ranging from 2 to
875 30 mg/day.

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

878 Overall, there was little difference in the incidence of discontinuation due to adverse
879 events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of
880 adverse events that led to discontinuation were similar between the aripiprazole and
881 placebo-treated patients.

882 **Adverse Findings Observed in Short-Term, Placebo-Controlled**
883 **Trials of Patients with Bipolar Mania**

884 The following findings are based on a pool of 3-week, placebo-controlled, bipolar mania
885 trials in which oral aripiprazole was administered at doses of 15 or 30 mg/day.

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

888 Overall, in patients with bipolar mania, there was little difference in the incidence of
889 discontinuation due to adverse events between aripiprazole-treated (11%) and placebo-
890 treated (9%) patients. The types of adverse events that led to discontinuation were similar
891 between the aripiprazole and placebo-treated patients.

892 **Commonly Observed Adverse Events in Short-Term, Placebo-**
893 **Controlled Trials of Patients with Bipolar Mania**

894 Commonly observed adverse events associated with the use of aripiprazole in patients
895 with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice

896 that for placebo) are shown in Table 1. There were no adverse events in the short-term
897 trials of schizophrenia that met these criteria.

Table 1: Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania in Patients Treated with Oral ABILIFY

Adverse Event	Percentage of Patients Reporting Event	
	Aripiprazole (n=597)	Placebo (n=436)
Accidental Injury	6	3
Constipation	13	6
Akathisia	15	4

898

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

902 Table 2 enumerates the pooled incidence, rounded to the nearest percent, of treatment-
903 emergent adverse events that occurred during acute therapy (up to 6 weeks in
904 schizophrenia and up to 3 weeks in bipolar mania), including only those events that
905 occurred in 2% or more of patients treated with aripiprazole (doses ≥ 2 mg/day) and for
906 which the incidence in patients treated with aripiprazole was greater than the incidence in
907 patients treated with placebo in the combined dataset.

908

Table 2: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials in Patients Treated with Oral ABILIFY

Body System Adverse Event	Percentage of Patients Reporting Event ^a	
	Aripiprazole (n=1523)	Placebo (n=849)
Body as a Whole		
Headache	31	26
Asthenia	8	7
Accidental Injury	5	4

Table 2: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials in Patients Treated with Oral ABILIFY

Body System Adverse Event	Percentage of Patients Reporting Event ^a	
	Aripiprazole (n=1523)	Placebo (n=849)
Peripheral Edema	2	1
Cardiovascular System		
Hypertension	2	1
Digestive System		
Nausea	16	12
Dyspepsia	15	13
Vomiting	11	6
Constipation	11	7
Musculoskeletal System		
Myalgia	4	3
Nervous System		
Agitation	25	24
Anxiety	20	17
Insomnia	20	15
Somnolence	12	8
Akathisia	12	5
Lightheadedness	11	8
Extrapyramidal Syndrome	6	4
Tremor	4	3
Increased Salivation	3	1
Respiratory System		
Pharyngitis	4	3
Rhinitis	4	3
Coughing	3	2
Special Senses		
Blurred Vision	3	1

^a Events reported by at least 2% of patients treated with oral aripiprazole, except the following events, which had an incidence equal to or less than placebo: abdominal pain, back pain, dental pain, diarrhea, dry mouth, anorexia, psychosis, hypertonia, upper respiratory tract infection, rash, vaginitis^f, dysmenorrhea^f.

^f Percentage based on gender total.

910 An examination of population subgroups did not reveal any clear evidence of
911 differential adverse event incidence on the basis of age, gender, or race.

912 **INTRAMUSCULAR ADMINISTRATION**

913 **Adverse Findings Observed in Short-Term, Placebo-Controlled** 914 **Trials of Patients with Agitation Associated with Schizophrenia** 915 **or Bipolar Mania**

916 The following findings are based on a pool of three placebo-controlled trials of patients
917 with agitation associated with schizophrenia or bipolar mania in which aripiprazole
918 injection was administered at doses of 5.25 mg to 15 mg.

919 **Adverse Events Associated with Discontinuation of Treatment in Short-** 920 **Term, Placebo-Controlled Trials**

921 Overall, in patients with agitation associated with schizophrenia or bipolar mania, there
922 was little difference in the incidence of discontinuation due to adverse events between
923 aripiprazole-treated (0.8%) and placebo-treated (0.5%) patients.

924 **Commonly Observed Adverse Events in Short-Term, Placebo-** 925 **Controlled Trials of Patients with Agitation Associated with** 926 **Schizophrenia or Bipolar Mania**

927 There was one commonly observed adverse event (nausea) associated with the use of
928 aripiprazole injection in patients with agitation associated with schizophrenia and bipolar
929 mania (incidence of 5% or greater and aripiprazole incidence at least twice that for
930 placebo).

931 **Adverse Events Occurring at an Incidence of 1% or More Among** 932 **Aripiprazole-Treated Patients and Greater than Placebo in Short-** 933 **Term, Placebo-Controlled Trials of Patients with Agitation** 934 **Associated with Schizophrenia or Bipolar Mania**

935 Table 3 enumerates the pooled incidence, rounded to the nearest percent, of treatment-
936 emergent adverse events that occurred during acute therapy (24 hour), including only
937 those events that occurred in 1% or more of patients treated with aripiprazole injection

938 (doses ≥ 5.25 mg/day) and for which the incidence in patients treated with aripiprazole
 939 injection was greater than the incidence in patients treated with placebo in the combined
 940 dataset.

941

Table 3: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials in Patients Treated with ABILIFY Injection

System Organ Class Primary Term	Percentage of Patients Reporting Event ^a	
	Aripiprazole (n=501)	Placebo (n=220)
Cardiac Disorders		
Tachycardia	2	<1
Gastrointestinal Disorders		
Nausea	9	3
Vomiting	3	1
Dyspepsia	1	<1
Dry Mouth	1	<1
General Disorders and Administration Site Conditions		
Fatigue	2	1
Investigations		
Blood Pressure Increased	1	<1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	1	<1
Nervous System Disorders		
Headache	12	7
Dizziness	8	5
Somnolence	7	4
Sedation	3	2
Akathisia	2	0

^a Events reported by at least 1% of patients treated with aripiprazole injection, except the following events, which had an incidence equal to or less than placebo: injection site pain, injection site burning, insomnia, agitation.

942

943 **Dose-Related Adverse Events**

944 **Schizophrenia**

945 Dose response relationships for the incidence of treatment-emergent adverse events were
946 evaluated from four trials in patients with schizophrenia comparing various fixed doses
947 (2, 10, 15, 20, and 30 mg/day) of oral aripiprazole to placebo. This analysis, stratified by
948 study, indicated that the only adverse event to have a possible dose response relationship,
949 and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg,
950 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

951 **Extrapyramidal Symptoms**

952 In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported
953 EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. In the short-term,
954 placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events
955 excluding events related to akathisia for aripiprazole-treated patients was 17% vs. 12%
956 for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of
957 akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo.
958 Objectively collected data from those trials was collected on the Simpson Angus Rating
959 Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of
960 Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the
961 objectively collected data did not show a difference between aripiprazole and placebo,
962 with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In
963 the bipolar mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale
964 showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61;
965 placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of
966 Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

967 Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia,
968 objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes
969 Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales
970 (for dyskinesias) did not show a difference between aripiprazole and placebo.

971 In the placebo-controlled trials in patients with agitation associated with
972 schizophrenia or bipolar mania, the incidence of reported EPS-related events excluding
973 events related to akathisia for aripiprazole-treated patients was 2% vs. 2% for placebo
974 and the incidence of akathisia-related events for aripiprazole-treated patients was 2% vs.
975 0% for placebo. Objectively collected data on the Simpson Angus Rating Scale (for EPS)

976 and the Barnes Akathisia Scale (for akathisia) for all treatment groups, did not show a
 977 difference between aripiprazole and placebo.

978 **Laboratory Test Abnormalities**

979 A between group comparison for 3- to 6-week, placebo-controlled trials revealed no
 980 medically important differences between the aripiprazole and placebo groups in the
 981 proportions of patients experiencing potentially clinically significant changes in routine
 982 serum chemistry, hematology, or urinalysis parameters. Similarly, there were no
 983 aripiprazole/placebo differences in the incidence of discontinuations for changes in serum
 984 chemistry, hematology, or urinalysis.

985 In a long-term (26-week), placebo-controlled trial there were no medically
 986 important differences between the aripiprazole and placebo patients in the mean change
 987 from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, and total cholesterol
 988 measurements.

989 **Weight Gain**

990 In 4- to 6- week trials in schizophrenia, there was a slight difference in mean weight gain
 991 between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively), and also a
 992 difference in the proportion of patients meeting a weight gain criterion of $\geq 7\%$ of body
 993 weight [aripiprazole (8%) compared to placebo (3%)]. In 3-week trials in mania, the
 994 mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. -0.2 kg,
 995 respectively. The proportion of patients meeting a weight gain criterion of $\geq 7\%$ of body
 996 weight was aripiprazole (3%) compared to placebo (2%).

997 Table 4 provides the weight change results from a long-term (26-week), placebo-
 998 controlled study of aripiprazole, both mean change from baseline and proportions of
 999 patients meeting a weight gain criterion of $\geq 7\%$ of body weight relative to baseline,
 1000 categorized by BMI at baseline:

Table 4: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample

BMI <23		BMI 23-27		BMI >27	
Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole

Table 4: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample

	BMI <23		BMI 23-27		BMI >27	
Mean change from baseline (kg)	-0.5	-0.5	-0.6	-1.3	-1.5	-2.1
% with ≥7% increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

1001

1002 Table 5 provides the weight change results from a long-term (52-week) study of
 1003 aripiprazole, both mean change from baseline and proportions of patients meeting a
 1004 weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at
 1005 baseline:

Table 5: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample

	BMI <23	BMI 23-27	BMI >27
Mean change from baseline (kg)	2.6	1.4	-1.2
% with ≥7% increase BW	30%	19%	8%

1006

1007 ECG Changes

1008 Between group comparisons for a pooled analysis of placebo-controlled trials in patients
 1009 with schizophrenia or bipolar mania, revealed no significant differences between oral
 1010 aripiprazole and placebo in the proportion of patients experiencing potentially important
 1011 changes in ECG parameters. Aripiprazole was associated with a median increase in heart
 1012 rate of 5 beats per minute compared to a 1 beat per minute increase among placebo
 1013 patients.

1014 In the pooled, placebo-controlled trials in patients with agitation associated with
 1015 schizophrenia or bipolar mania, there were no significant differences between
 1016 aripiprazole injection and placebo in the proportion of patients experiencing potentially
 1017 important changes in ECG parameters, as measured by standard 12-lead ECGs.

1018 Additional Findings Observed in Clinical Trials

1019 **Adverse Events in Long-Term, Double-Blind, Placebo-Controlled Trials**

1020 The adverse events reported in a 26-week, double-blind trial comparing oral ABILIFY
1021 and placebo in patients with schizophrenia were generally consistent with those reported
1022 in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9%
1023 (13/153) for ABILIFY vs. 1% (2/153) for placebo]. In this study, the majority of the
1024 cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in
1025 therapy (9/13 \leq 49 days), and were of limited duration (9/13 \leq 10 days). Tremor
1026 infrequently led to discontinuation ($<$ 1%) of ABILIFY. In addition, in a long-term (52-
1027 week), active-controlled study, the incidence of tremor for ABILIFY was 4% (34/859). A
1028 similar adverse event profile was observed in a long-term study in bipolar disorder.

1029 **Other Adverse Events Observed During the Premarketing** 1030 **Evaluation of Oral Aripiprazole**

1031 Following is a list of modified COSTART terms that reflect treatment-emergent adverse
1032 events as defined in the introduction to the **ADVERSE REACTIONS** section reported
1033 by patients treated with oral aripiprazole at multiple doses \geq 2 mg/day during any phase of
1034 a trial within the database of 7951 patients. All reported events are included except those
1035 already listed in Table 2, or other parts of the **ADVERSE REACTIONS** section, those
1036 considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so
1037 general as to be uninformative, events reported with an incidence of \leq 0.05% and which
1038 did not have a substantial probability of being acutely life-threatening, events that are
1039 otherwise common as background events, and events considered unlikely to be drug
1040 related. It is important to emphasize that, although the events reported occurred during
1041 treatment with aripiprazole, they were not necessarily caused by it.

1042 Events are further categorized by body system and listed in order of decreasing
1043 frequency according to the following definitions: frequent adverse events are those
1044 occurring in at least 1/100 patients (only those not already listed in the tabulated results
1045 from placebo-controlled trials appear in this listing); infrequent adverse events are those
1046 occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than
1047 1/1000 patients.

1048 *Body as a Whole: Frequent* - flu syndrome, fever, chest pain, rigidity (including
1049 neck and extremity), neck pain, pelvic pain; *Infrequent* - face edema, suicide attempt,

1050 malaise, migraine, chills, photosensitivity, tightness (including abdomen, back, extremity,
1051 head, jaw, neck, and tongue), jaw pain, bloating, enlarged abdomen, chest tightness,
1052 throat pain; *Rare* - moniliasis, head heaviness, throat tightness, Mendelson's syndrome,
1053 heat stroke.

1054 *Cardiovascular System: Frequent* - tachycardia (including ventricular and
1055 supraventricular), hypotension, bradycardia; *Infrequent* - palpitation, hemorrhage, heart
1056 failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT
1057 interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris,
1058 pallor, cardiopulmonary arrest, phlebitis; *Rare* - bundle branch block, atrial flutter,
1059 vasovagal reaction, cardiomegaly, thrombophlebitis, cardiopulmonary failure.

1060 *Digestive System: Frequent* - nausea and vomiting; *Infrequent* - increased
1061 appetite, dysphagia, gastroenteritis, flatulence, tooth caries, gastritis, gingivitis,
1062 gastrointestinal hemorrhage, hemorrhoids, gastroesophageal reflux, periodontal abscess,
1063 fecal incontinence, rectal hemorrhage, stomatitis, colitis, tongue edema, cholecystitis,
1064 mouth ulcer, oral moniliasis, eructation, fecal impaction, cholelithiasis; *Rare* -
1065 esophagitis, hematemesis, intestinal obstruction, gum hemorrhage, hepatitis, peptic ulcer,
1066 glossitis, melena, duodenal ulcer, cheilitis, hepatomegaly, pancreatitis.

1067 *Endocrine System: Infrequent* - hypothyroidism; *Rare* - goiter, hyperthyroidism.

1068 *Hemic/Lymphatic System: Frequent* - ecchymosis, anemia; *Infrequent* -
1069 hypochromic anemia, leukocytosis, leukopenia (including neutropenia),
1070 lymphadenopathy, eosinophilia, macrocytic anemia; *Rare* - thrombocytopenia,
1071 thrombocytopenia, petechiae.

1072 *Metabolic and Nutritional Disorders: Frequent* - weight loss, creatine
1073 phosphokinase increased, dehydration, *Infrequent* - edema, hyperglycemia,
1074 hypercholesteremia, hypokalemia, diabetes mellitus, hypoglycemia, hyperlipemia, SGPT
1075 increased, thirst, BUN increased, hyponatremia, SGOT increased, creatinine increased,
1076 cyanosis, alkaline phosphatase increased, bilirubinemia, iron deficiency anemia,
1077 hyperkalemia, hyperuricemia, obesity; *Rare* - lactic dehydrogenase increased,
1078 hypernatremia, gout, hypoglycemic reaction.

1079 *Musculoskeletal System: Frequent* - muscle cramp; *Infrequent* - arthralgia,
1080 myasthenia, arthrosis, bone pain, arthritis, muscle weakness, spasm, bursitis, myopathy;
1081 *Rare* - rheumatoid arthritis, rhabdomyolysis, tendonitis, tenosynovitis.

1082 *Nervous System: Frequent* - depression, nervousness, schizophrenic reaction,
1083 hallucination, hostility, confusion, paranoid reaction, suicidal thought, abnormal gait,
1084 manic reaction, delusions, abnormal dream; *Infrequent* - emotional lability, twitch,
1085 cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence,
1086 extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, panic attack,
1087 decreased libido, hypersomnia, dyskinesia, manic depressive reaction, ataxia, visual
1088 hallucination, cerebrovascular accident, hypokinesia, depersonalization, impaired
1089 memory, delirium, dysarthria, tardive dyskinesia, amnesia, hyperactivity, increased
1090 libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia,
1091 increased reflexes, akinesia, decreased consciousness, hyperesthesia, slowed thinking;
1092 *Rare* - blunted affect, euphoria, incoordination, oculogyric crisis, obsessive thought,
1093 hypotonia, buccoglossal syndrome, decreased reflexes, derealization, intracranial
1094 hemorrhage.

1095 *Respiratory System: Frequent* - sinusitis, dyspnea, pneumonia, asthma;
1096 *Infrequent* - epistaxis, hiccup, laryngitis, aspiration pneumonia; *Rare* - pulmonary edema,
1097 increased sputum, pulmonary embolism, hypoxia, respiratory failure, apnea, dry nasal
1098 passages, hemoptysis.

1099 *Skin and Appendages: Frequent* - skin ulcer, sweating, dry skin; *Infrequent* -
1100 pruritus, vesiculobullous rash, acne, eczema, skin discoloration, alopecia, seborrhea,
1101 psoriasis; *Rare* - maculopapular rash, exfoliative dermatitis, urticaria.

1102 *Special Senses: Frequent* - conjunctivitis; *Infrequent* - ear pain, dry eye, eye pain,
1103 tinnitus, cataract, otitis media, altered taste, blepharitis, eye hemorrhage, deafness; *Rare* -
1104 diplopia, frequent blinking, ptosis, otitis externa, amblyopia, photophobia.

1105 *Urogenital System: Frequent* - urinary incontinence; *Infrequent* - urinary
1106 frequency, leukorrhea, urinary retention, cystitis, hematuria, dysuria, amenorrhea, vaginal
1107 hemorrhage, abnormal ejaculation, kidney failure, vaginal moniliasis, urinary urgency,
1108 gynecomastia, kidney calculus, albuminuria, breast pain, urinary burning; *Rare* -
1109 nocturia, polyuria, menorrhagia, anorgasmy, glycosuria, cervicitis, uterus hemorrhage,
1110 female lactation, urolithiasis, priapism.

1111 **Other Adverse Events Observed During the Premarketing**
1112 **Evaluation of Aripiprazole Injection**

1113 Following is a list of MedDRA terms that reflect treatment-emergent adverse events as
1114 defined in the introduction to the **ADVERSE REACTIONS** section reported by patients
1115 treated with aripiprazole injection at doses ≥ 1 mg/day during any phase of a trial within
1116 the database of 749 patients. All reported events are included except those already listed
1117 in Table 2 or 3, or other parts of the **ADVERSE REACTIONS** section, those considered
1118 in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to
1119 be uninformative, events reported with an incidence of $\leq 0.05\%$ and which did not have a
1120 substantial probability of being acutely life-threatening, events that are otherwise
1121 common as background events, and events considered unlikely to be drug related. It is
1122 important to emphasize that, although the events reported occurred during treatment with
1123 aripiprazole injection, they were not necessarily caused by it.

1124 Events are further categorized by MedDRA system organ class and listed in order
1125 of decreasing frequency according to the following definitions: frequent adverse events
1126 are those occurring in at least 1/100 patients (only those not already listed in the tabulated
1127 results from placebo-controlled trials appear in this listing); infrequent adverse events are
1128 those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than
1129 1/1000 patients.

1130 *Cardiac Disorders: Infrequent* - sinus tachycardia.

1131 *Ear and Labyrinth Disorders: Infrequent* - hyperacusis.

1132 *Gastrointestinal Disorders: Infrequent* - aptyalism, oral hypoaesthesia.

1133 *General Disorders and Administration Site Conditions: Infrequent* - hot feeling,
1134 injection site stinging, abnormal feeling, injection site pruritus, injection site swelling,
1135 venipuncture site bruise.

1136 *Infections and Infestations: Infrequent* - bacteruria, urinary tract infection,
1137 urosepsis.

1138 *Injury, Poisoning and Procedural Complications: Infrequent* - skin laceration.

1139 *Investigations: Infrequent* - heart rate increased, blood pressure decreased, blood
1140 pressure abnormal, heart rate irregular, blood glucose increased, body temperature
1141 increased, electrocardiogram T-wave abnormal, heart rate decreased.

1142 *Musculoskeletal and Connective Tissue Disorders: Infrequent* - buttock pain,
1143 chest wall pain, groin pain, muscle rigidity, muscle tightness, sensation of heaviness.

1144 *Nervous System Disorders: Infrequent* - dementia, dysgeusia, lethargy,
1145 parkinsonism.

1146 *Psychiatric Disorders: Infrequent* - auditory hallucination, intentional self-injury,
1147 nightmare, tension.

1148 *Reproductive System and Breast Disorders: Infrequent* - erectile dysfunction.

1149 *Respiratory, Thoracic and Mediastinal Disorders: Infrequent* - pharyngolaryngeal
1150 pain, nasal congestion, rhinorrhoea.

1151 *Vascular Disorders: Infrequent* - flushing, blood pressure fluctuation.

1152 **Other Events Observed During the Postmarketing Evaluation of** 1153 **Aripiprazole**

1154 Voluntary reports of adverse events in patients taking aripiprazole that have been
1155 received since market introduction and not listed above that may have no causal
1156 relationship with the drug include rare occurrences of allergic reaction (eg, anaphylactic
1157 reaction, angioedema, laryngospasm, pruritis, or urticaria).

1158 **DRUG ABUSE AND DEPENDENCE**

1159 **Controlled Substance**

1160 ABILIFY (aripiprazole) is not a controlled substance.

1161 **Abuse and Dependence**

1162 Aripiprazole has not been systematically studied in humans for its potential for abuse,
1163 tolerance, or physical dependence. In physical dependence studies in monkeys,

1164 withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical
1165 trials did not reveal any tendency for any drug-seeking behavior, these observations were
1166 not systematic and it is not possible to predict on the basis of this limited experience the
1167 extent to which a CNS-active drug will be misused, diverted, and/or abused once
1168 marketed. Consequently, patients should be evaluated carefully for a history of drug
1169 abuse, and such patients should be observed closely for signs of ABILIFY misuse or
1170 abuse (eg, development of tolerance, increases in dose, drug-seeking behavior).

1171 **OVERDOSAGE**

1172 MedDRA terminology has been used to classify the adverse events.

1173 **Human Experience**

1174 A total of 76 cases of deliberate or accidental overdosage with oral aripiprazole have
1175 been reported worldwide. These include overdoses with oral aripiprazole alone and in
1176 combination with other substances. No fatality was reported from these cases. Of the 44
1177 cases with known outcome, 33 recovered without sequelae and one recovered with
1178 sequelae (mydriasis and feeling abnormal). The largest known acute ingestion with a
1179 known outcome involved 1080 mg of oral aripiprazole (36 times the maximum
1180 recommended daily dose) in a patient who fully recovered. Included in the 76 cases are
1181 10 cases of deliberate or accidental overdosage in children (age 12 and younger)
1182 involving oral aripiprazole ingestions up to 195 mg with no fatalities.

1183 Common adverse events (reported in at least 5% of all overdose cases) reported
1184 with oral aripiprazole overdosage (alone or in combination with other substances) include
1185 vomiting, somnolence, and tremor. Other clinically important signs and symptoms
1186 observed in one or more patients with aripiprazole overdoses (alone or with other
1187 substances) include acidosis, aggression, aspartate aminotransferase increased, atrial
1188 fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine
1189 phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia,
1190 hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged,
1191 pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

1192 **Management of Overdosage**

1193 No specific information is available on the treatment of overdose with aripiprazole. An
1194 electrocardiogram should be obtained in case of overdosage and, if QTc interval
1195 prolongation is present, cardiac monitoring should be instituted. Otherwise, management
1196 of overdose should concentrate on supportive therapy, maintaining an adequate airway,
1197 oxygenation and ventilation, and management of symptoms. Close medical supervision
1198 and monitoring should continue until the patient recovers.

1199 *Charcoal:* In the event of an overdose of ABILIFY, an early charcoal
1200 administration may be useful in partially preventing the absorption of aripiprazole.
1201 Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of
1202 aripiprazole, decreased the mean AUC and Cmax of aripiprazole by 50%.

1203 *Hemodialysis:* Although there is no information on the effect of hemodialysis in
1204 treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose
1205 management since aripiprazole is highly bound to plasma proteins.

1206 **DOSAGE AND ADMINISTRATION**

1207 **Oral**

1208 **Schizophrenia**

1209 ***Usual Dose***

1210 The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered
1211 on a once-a-day schedule without regard to meals. ABILIFY has been systematically
1212 evaluated and shown to be effective in a dose range of 10 to 30 mg/day, when
1213 administered as the tablet formulation, however, doses higher than 10 or 15 mg/day, the
1214 lowest doses in these trials, were not more effective than 10 or 15 mg/day. Dosage
1215 increases should not be made before 2 weeks, the time needed to achieve steady state.

1216 **Dosage in Special Populations**

1217 Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal
1218 or hepatic impairment status (see **CLINICAL PHARMACOLOGY: Special**
1219 **Populations**).

1220 *Dosage adjustment for patients taking aripiprazole concomitantly with potential*
1221 *CYP3A4 inhibitors:* When concomitant administration of ketoconazole with aripiprazole
1222 occurs, aripiprazole dose should be reduced to one-half of the usual dose. When the
1223 CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should
1224 then be increased.

1225 *Dosage adjustment for patients taking aripiprazole concomitantly with potential*
1226 *CYP2D6 inhibitors:* When concomitant administration of potential CYP2D6 inhibitors
1227 such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose
1228 should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is
1229 withdrawn from the combination therapy, aripiprazole dose should then be increased.

1230 *Dosage adjustment for patients taking potential CYP3A4 inducers:* When a
1231 potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the
1232 aripiprazole dose should be doubled (to 20 or 30 mg). Additional dose increases should
1233 be based on clinical evaluation. When carbamazepine is withdrawn from the combination
1234 therapy, the aripiprazole dose should be reduced to 10 to 15 mg.

1235 **Maintenance Therapy**

1236 While there is no body of evidence available to answer the question of how long a patient
1237 treated with aripiprazole should remain on it, systematic evaluation of patients with
1238 schizophrenia who had been symptomatically stable on other antipsychotic medications
1239 for periods of 3 months or longer, were discontinued from those medications, and were
1240 then administered ABILIFY 15 mg/day and observed for relapse during a period of up to
1241 26 weeks, demonstrated a benefit of such maintenance treatment (see **CLINICAL**
1242 **PHARMACOLOGY: Clinical Studies**). Patients should be periodically reassessed to
1243 determine the need for maintenance treatment.

1244 **Switching from Other Antipsychotics**

1245 There are no systematically collected data to specifically address switching patients with
1246 schizophrenia from other antipsychotics to ABILIFY or concerning concomitant
1247 administration with other antipsychotics. While immediate discontinuation of the
1248 previous antipsychotic treatment may be acceptable for some patients with schizophrenia,
1249 more gradual discontinuation may be most appropriate for others. In all cases, the period
1250 of overlapping antipsychotic administration should be minimized.

1251 **Bipolar Disorder**1252 ***Usual Dose***

1253 In clinical trials, the starting dose was 30 mg given once a day. A dose of 30 mg/day was
1254 found to be effective when administered as the tablet formulation. Approximately 15% of
1255 patients had their dose decreased to 15 mg based on assessment of tolerability. The safety
1256 of doses above 30 mg/day has not been evaluated in clinical trials.

1257 **Dosage in Special Populations**

1258 See *Dosage in Special Populations* under **DOSAGE AND ADMINISTRATION:**
1259 **Schizophrenia.**

1260 **Maintenance Therapy**

1261 While there is no body of evidence available to answer the question of how long a patient
1262 treated with aripiprazole should remain on it, patients with Bipolar I Disorder who had
1263 been symptomatically stable on ABILIFY Tablets (15 mg/day or 30 mg/day with a
1264 starting dose of 30 mg/day) for at least 6 consecutive weeks and then randomized to
1265 ABILIFY Tablets (15 mg/day or 30 mg/day) or placebo and monitored for relapse,
1266 demonstrated a benefit of such maintenance treatment (see **CLINICAL**
1267 **PHARMACOLOGY: Clinical Studies**). While it is generally agreed that
1268 pharmacological treatment beyond an acute response in mania is desirable, both for
1269 maintenance of the initial response and for prevention of new manic episodes, there are
1270 no systematically obtained data to support the use of aripiprazole in such longer-term
1271 treatment (ie, beyond 6 weeks).

1272 **Oral Solution**

1273 The oral solution can be given on a mg-per-mg basis in place of the 5-, 10-, 15-, or 20-mg
1274 tablet strengths. Solution doses can be substituted for the tablet doses on a mg-per-mg
1275 basis up to 25 mg of the tablet. Patients receiving 30-mg tablets should receive 25 mg of
1276 the solution (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

1277 **Directions for Use of ABILIFY DISCMELT Orally Disintegrating**
1278 **Tablets**

1279 **Patients should be told the following:**

1280 Do not open the blister until ready to administer. For single tablet removal, open the
1281 package and peel back the foil on the blister to expose the tablet. Do not push the tablet
1282 through the foil because this could damage the tablet. Immediately upon opening the
1283 blister, using dry hands, remove the tablet and place the entire ABILIFY DISCMELT
1284 orally disintegrating tablet on the tongue. Tablet disintegration occurs rapidly in saliva. It
1285 is recommended that ABILIFY DISCMELT be taken without liquid. However, if needed,
1286 it can be taken with liquid. Do not attempt to split the tablet.

1287 **Intramuscular Injection**

1288 **Agitation Associated with Schizophrenia or Bipolar Mania**

1289 ***Usual Dose***

1290 The efficacy of aripiprazole injection in controlling agitation in these disorders was
1291 demonstrated in a dose range of 5.25 mg to 15 mg. The recommended dose in these
1292 patients is 9.75 mg. No additional benefit was demonstrated for 15 mg compared to 9.75
1293 mg. A lower dose of 5.25 mg may be considered when clinical factors warrant. If
1294 agitation warranting a second dose persists following the initial dose, cumulative doses
1295 up to a total of 30 mg/day may be given. However, the efficacy of repeated doses of
1296 aripiprazole injection in agitated patients has not been systematically evaluated in
1297 controlled clinical trials. Also, the safety of total daily doses greater than 30 mg or
1298 injections given more frequently than every 2 hours have not been adequately evaluated
1299 in clinical trials.

1300 If ongoing aripiprazole therapy is clinically indicated, oral aripiprazole in a range of 10
1301 mg to 30 mg/day should replace aripiprazole injection as soon as possible (see
1302 **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION:**
1303 **Schizophrenia or Bipolar Disorder**).

1304 **Administration of ABILIFY Injection**

1305 To administer ABILIFY Injection, draw up the required volume of solution into the
 1306 syringe as shown in Table 6. Discard any unused portion.

Table 6: ABILIFY Injection Dosing Recommendations

Single-Dose	Required Volume of Solution
5.25 mg	0.7 mL
9.75 mg	1.3 mL
15 mg	2 mL

1307 ABILIFY Injection is intended for intramuscular use only. Do not administer
 1308 intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

1309 Parenteral drug products should be inspected visually for particulate matter and
 1310 discoloration prior to administration, whenever solution and container permit.

1311 **Dosage in Special Populations**

1312 See *Dosage in Special Populations* under **DOSAGE AND ADMINISTRATION:**
 1313 **Schizophrenia.**

1314 **ANIMAL TOXICOLOGY**

1315 Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity
 1316 study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and
 1317 60 mg/kg. The 40- and 60-mg/kg doses are 13 and 19 times the maximum recommended
 1318 human dose (MRHD) based on mg/m^2 and 7 to 14 times human exposure at MRHD
 1319 based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal
 1320 evidence of retinal degeneration. Additional studies to further evaluate the mechanism
 1321 have not been performed. The relevance of this finding to human risk is unknown.

1322 **HOW SUPPLIED**

1323 ABILIFY[®] (aripiprazole) Tablets have markings on one side and are available in the
 1324 strengths and packages listed in Table 7.

Table 7: ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
2 mg	green modified rectangle	"A-006" and "2"	Bottle of 30	59148-006-13
			Blister of 100	59148-006-35
5 mg	blue modified rectangle	"A-007" and "5"	Bottle of 30	59148-007-13
			Blister of 100	59148-007-35
10 mg	pink modified rectangle	"A-008" and "10"	Bottle of 30	59148-008-13
			Blister of 100	59148-008-35
15 mg	yellow round	"A-009" and "15"	Bottle of 30	59148-009-13
			Blister of 100	59148-009-35
20 mg	white round	"A-010" and "20"	Bottle of 30	59148-010-13
			Blister of 100	59148-010-35
30 mg	pink round	"A-011" and "30"	Bottle of 30	59148-011-13
			Blister of 100	59148-011-35

1325

1326 ABILIFY[®] DISCMELT[™] (aripiprazole) Orally Disintegrating Tablets are round tablets
 1327 with markings on either side. ABILIFY DISCMELT is available in the strengths and
 1328 packages listed in Table 8.

Table 8: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations

Tablet Strength	Tablet Color	Tablet Markings	Pack Size	NDC Code
10 mg	pink (with scattered specks)	"A" and "640" "10"	Blister of 30	59148-640-23
15 mg	yellow (with scattered specks)	"A" and "641" "15"	Blister of 30	59148-641-23

1329

1330 ABILIFY[®] (aripiprazole) Oral Solution (1 mg/mL) is supplied in child-resistant bottles
 1331 along with a calibrated oral dosing cup. ABILIFY oral solution is available as follows:

1332 150-mL bottle NDC 59148-013-15

1333 ABILIFY[®] (aripiprazole) Injection for intramuscular use is available as a ready-to-use,
1334 9.75 mg/1.3 mL (7.5 mg/mL) solution in clear, Type 1 glass vials as follows:

1335 9.75 mg/1.3 mL single-dose vial NDC 59148-016-65

1336 **Storage**

1337 **Tablets**

1338 Store at 25° C (77° F); excursions permitted between 15° C to 30° C (59° F to 86° F) [see
1339 USP Controlled Room Temperature].

1340 **Oral Solution**

1341 Store at 25° C (77° F); excursions permitted between 15° C to 30° C (59° F to 86° F) [see
1342 USP Controlled Room Temperature]. Opened bottles of ABILIFY oral solution can be
1343 used for up to 6 months after opening, but not beyond the expiration date on the bottle.
1344 The bottle and its contents should be discarded after the expiration date.

1345 **Injection**

1346 Store at 25° C (77° F); excursions permitted to 15° C to 30° C (59° F to 86° F) [see USP
1347 Controlled Room Temperature]. Protect from light by storing in the original container.
1348 Retain in carton until time of use.

1349 Tablets manufactured by Otsuka Pharmaceutical Co, Ltd, Tokyo, 101-8535 Japan or
1350 Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

1351 Orally disintegrating tablets manufactured by Bristol-Myers Squibb Company, Princeton,
1352 NJ 08543 USA

1353 Oral solution and Injection are manufactured by Bristol-Myers Squibb Company,
1354 Princeton, NJ 08543 USA

1355 Distributed and marketed by Otsuka America Pharmaceutical, Inc, Rockville, MD 20850
1356 USA

1357 Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

1358 US Patent Nos: 5,006,528 and 6,977,257



Bristol-Myers Squibb Company



Otsuka America Pharmaceutical, Inc.

1359 1156731XX 1158571XX 1191707XX XXXX/XX-XX Revised _____

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