

# ABILIFY<sup>®</sup> (aripiprazole)

ABILIFY<sup>®</sup> (aripiprazole) Tablets

ABILIFY<sup>®</sup> DISCMELT<sup>™</sup> (aripiprazole) Orally Disintegrating Tablets

ABILIFY<sup>®</sup> (aripiprazole) Oral Solution

ABILIFY<sup>®</sup> (aripiprazole) Injection FOR INTRAMUSCULAR USE ONLY

## WARNING

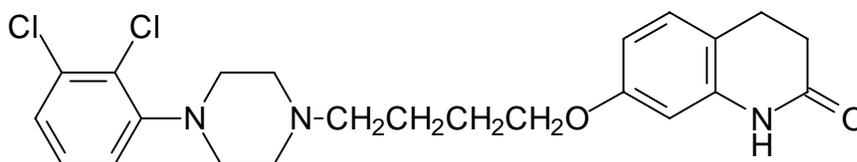
### Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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 is not approved for the treatment of patients with dementia-related psychosis.

## DESCRIPTION

Aripiprazole is a psychotropic drug that is available as ABILIFY<sup>®</sup> (aripiprazole) tablets, ABILIFY<sup>®</sup> DISCMELT<sup>™</sup> (aripiprazole) orally disintegrating tablets, ABILIFY<sup>®</sup> (aripiprazole) oral solution, and ABILIFY<sup>®</sup> (aripiprazole) injection, a solution for intramuscular injection. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl. The empirical formula is C<sub>23</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> 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  
33 ferric 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  $\beta$ -  
48 cyclodextrin (SBECD), tartaric acid, sodium hydroxide, and water for injection.

## 49 **CLINICAL PHARMACOLOGY**

### 50 **Pharmacodynamics**

51 Aripiprazole exhibits high affinity for dopamine D<sub>2</sub> and D<sub>3</sub>, serotonin 5-HT<sub>1A</sub> and 5-  
52 HT<sub>2A</sub> receptors (K<sub>i</sub> values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity

53 for dopamine D<sub>4</sub>, serotonin 5-HT<sub>2C</sub> and 5-HT<sub>7</sub>, alpha<sub>1</sub>-adrenergic and histamine H<sub>1</sub>  
54 receptors (K<sub>i</sub> values of 44, 15, 39, 57, and 61 nM, respectively), and moderate affinity for  
55 the serotonin reuptake site (K<sub>i</sub>=98 nM). Aripiprazole has no appreciable affinity for  
56 cholinergic muscarinic receptors (IC<sub>50</sub>>1000 nM). Aripiprazole functions as a partial  
57 agonist at the dopamine D<sub>2</sub> and the serotonin 5-HT<sub>1A</sub> receptors, and as an antagonist at  
58 serotonin 5-HT<sub>2A</sub> 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 D<sub>2</sub> and 5-HT<sub>1A</sub> receptors  
63 and antagonist activity at 5-HT<sub>2A</sub> receptors. Actions at receptors other than D<sub>2</sub>, 5-HT<sub>1A</sub>,  
64 and 5-HT<sub>2A</sub> 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 alpha<sub>1</sub> receptors.

## 67 **Pharmacokinetics**

68 ABILIFY (aripiprazole) activity is presumably primarily due to the parent drug,  
69 aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which  
70 has been shown to have affinities for D<sub>2</sub> receptors similar to the parent drug and  
71 represents 40% of the parent drug exposure in plasma. The mean elimination half-lives  
72 are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively.  
73 Steady-state 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<sub>max</sub> or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed  
88 T<sub>max</sub> 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<sub>max</sub> 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 D<sub>2</sub> 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 [<sup>14</sup>C]-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 two 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<sub>max</sub> 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<sub>max</sub> 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<sub>max</sub> 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 H<sub>2</sub> 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<sub>max</sub> 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<sub>max</sub> 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<sub>max</sub> 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 (aripiprazole) in the treatment of schizophrenia was evaluated  
248 in five short-term (4- and 6-week), placebo-controlled trials of acutely relapsed inpatients  
249 who predominantly met DSM-III/IV criteria for schizophrenia. Four of the five trials  
250 were able to distinguish aripiprazole from placebo, but one study, the smallest, did not.  
251 Three of these studies also included an active control group consisting of either  
252 risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for  
253 a comparison of ABILIFY and the active comparators.

254 In the four 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 6-week trial (n=367) comparing three fixed doses of ABILIFY (2, 5, or 10  
279 mg/day) to placebo, the 10-mg dose of ABILIFY was superior to placebo in the PANSS  
280 total score, the primary outcome measure of the study. The 2-mg and 5-mg doses did not  
281 demonstrate superiority to placebo on the primary outcome measure.

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

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

289 Thus, the efficacy of 10-mg, 15-mg, 20-mg, and 30-mg daily doses was  
290 established in two studies for each dose. Among these doses, there was no evidence that  
291 the higher dose groups offered any advantage over the lowest dose group of these studies.

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

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

## 304 **Bipolar Disorder**

305 The efficacy of ABILIFY in the treatment of acute manic episodes was established in two  
306 3-week, placebo-controlled trials in hospitalized patients who met the DSM-IV criteria  
307 for Bipolar I Disorder with manic or mixed episodes (in one trial, 21% of placebo and  
308 42% of ABILIFY-treated patients had data beyond two weeks). These trials included  
309 patients with or without psychotic features and with or without a rapid-cycling course.

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

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

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

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

### 339 **Agitation Associated with Schizophrenia or Bipolar Mania**

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

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

362 (1) In a placebo-controlled trial in agitated inpatients predominantly meeting  
363 DSM-IV criteria for schizophrenia (n=350), four fixed aripiprazole injection doses of 1  
364 mg, 5.25 mg, 9.75 mg, and 15 mg were evaluated. At 2 hours post-injection, the 5.25-mg,  
365 9.75-mg, and 15-mg doses were statistically superior to placebo in the PANSS Excited  
366 Component and on the CGI-I scale.

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

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

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

379 **INDICATIONS AND USAGE**

380 **Schizophrenia**

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

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

392 **Bipolar Disorder**

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

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

399 The efficacy of ABILIFY in maintaining efficacy in patients with Bipolar I  
400 Disorder with a recent manic or mixed episode who had been stabilized and then  
401 maintained for at least 6 weeks, was demonstrated in a double-blind, placebo-controlled  
402 trial. Prior to entering the double-blind, randomization phase of this trial, patients were  
403 clinically stabilized and maintained their stability for 6 consecutive weeks on ABILIFY.  
404 Following this 6-week maintenance phase, patients were randomized to either placebo or  
405 ABILIFY and monitored for relapse (see **CLINICAL PHARMACOLOGY: Clinical**  
406 **Studies**). Physicians who elect to use ABILIFY for extended periods, that is, longer than  
407 6 weeks, should periodically re-evaluate the long-term usefulness of the drug for the  
408 individual patient (see **DOSAGE AND ADMINISTRATION**).

## 409 **Agitation Associated with Schizophrenia or Bipolar Mania**

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

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

## 421 **CONTRAINDICATIONS**

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

## 423 **WARNINGS**

### 424 **Increased Mortality in Elderly Patients with Dementia-Related** 425 **Psychosis**

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

### 430 **Neuroleptic Malignant Syndrome (NMS)**

431 A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant  
432 Syndrome (NMS) has been reported in association with administration of antipsychotic  
433 drugs, including aripiprazole. Rare cases of NMS occurred during aripiprazole treatment  
434 in the worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia,  
435 muscle rigidity, altered mental status, and evidence of autonomic instability (irregular  
436 pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional

437 signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis),  
438 and acute renal failure.

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

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

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

## 453 **Tardive Dyskinesia**

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

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

465 There is no known treatment for established cases of tardive dyskinesia, although  
466 the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.  
467 Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs

468 and symptoms of the syndrome and, thereby, may possibly mask the underlying process.  
469 The effect that symptomatic suppression has upon the long-term course of the syndrome  
470 is unknown.

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

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

## 482 **Cerebrovascular Adverse Events, Including Stroke, in Elderly** 483 **Patients with Dementia-Related Psychosis**

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

## 494 **Hyperglycemia and Diabetes Mellitus**

495 Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar  
496 coma or death, has been reported in patients treated with atypical antipsychotics. There  
497 have been few reports of hyperglycemia in patients treated with ABILIFY. Although  
498 fewer patients have been treated with ABILIFY, it is not known if this more limited

499 experience is the sole reason for the paucity of such reports. Assessment of the  
500 relationship between atypical antipsychotic use and glucose abnormalities is complicated  
501 by the possibility of an increased background risk of diabetes mellitus in patients with  
502 schizophrenia and the increasing incidence of diabetes mellitus in the general population.  
503 Given these confounders, the relationship between atypical antipsychotic use and  
504 hyperglycemia-related adverse events is not completely understood. However,  
505 epidemiological studies which did not include ABILIFY suggest an increased risk of  
506 treatment-emergent hyperglycemia-related adverse events in patients treated with the  
507 atypical antipsychotics included in these studies. Because ABILIFY was not marketed at  
508 the time these studies were performed, it is not known if ABILIFY is associated with this  
509 increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients  
510 treated with atypical antipsychotics are not available.

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

## 522 **PRECAUTIONS**

### 523 **General**

#### 524 **Orthostatic Hypotension**

525 Aripiprazole may be associated with orthostatic hypotension, perhaps due to its  $\alpha_1$ -  
526 adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated  
527 events from five short-term, placebo-controlled trials in schizophrenia (n=926) on oral  
528 ABILIFY included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), postural  
529 dizziness (placebo 0.7%, aripiprazole 0.8%), and syncope (placebo 1%, aripiprazole

530 0.6%). The incidence of orthostatic hypotension-associated events from short-term,  
531 placebo-controlled trials in bipolar mania (n=597) on oral ABILIFY included: orthostatic  
532 hypotension (placebo 0%, aripiprazole 0.7%), postural dizziness (placebo 0.2%,  
533 aripiprazole 0.5%), and syncope (placebo 0.7%, aripiprazole 0.3%). The incidence of  
534 orthostatic hypotension-associated events from short-term, placebo-controlled trials in  
535 agitation associated with schizophrenia or bipolar mania (n=501) on ABILIFY Injection  
536 included: orthostatic hypotension (placebo 0%, aripiprazole 0.6%), postural dizziness  
537 (placebo 0.5%, aripiprazole 0.2%), and syncope (placebo 0%, aripiprazole 0.4%).

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

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

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

### 555 **Seizure/Convulsion**

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

561 or bipolar mania, 0.2% (1/501) of aripiprazole injection-treated patients and 0% (0/220)  
562 of placebo-treated patients experienced seizures.

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

### 567 **Potential for Cognitive and Motor Impairment**

568 ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking,  
569 or motor skills. For example, in short-term, placebo-controlled trials of schizophrenia,  
570 somnolence (including sedation) was reported in 10% of patients on oral ABILIFY  
571 compared to 8% of patients on placebo. Somnolence (including sedation) led to  
572 discontinuation in 0.1% (1/926) of patients with schizophrenia on oral ABILIFY in short-  
573 term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar mania,  
574 somnolence (including sedation) was reported in 14% of patients on oral ABILIFY  
575 compared to 7% of patients on placebo, but did not lead to discontinuation of any patients  
576 with bipolar mania. In short-term, placebo-controlled trials of patients with agitation  
577 associated with schizophrenia or bipolar mania, somnolence (including sedation) was  
578 reported in 9% of patients on ABILIFY Injection compared to 6% of patients on placebo.  
579 Somnolence (including sedation) did not lead to discontinuation of any patients with  
580 agitation associated with schizophrenia or bipolar mania.

581 Despite the relatively modest increased incidence of somnolence compared to  
582 placebo, patients should be cautioned about operating hazardous machinery, including  
583 automobiles, until they are reasonably certain that therapy with ABILIFY does not affect  
584 them adversely.

### 585 **Body Temperature Regulation**

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

591 **Dysphagia**

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

598 **Suicide**

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

603 **Use in Patients with Concomitant Illness**

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

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

610 *Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's*  
611 *Disease:* In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients  
612 with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range:  
613 56-99 years), the treatment-emergent adverse events that were reported at an incidence of  
614  $\geq 3\%$  and aripiprazole incidence at least twice that for placebo were lethargy [placebo 2%,  
615 aripiprazole 5%], somnolence (including sedation) [placebo 3%, aripiprazole 8%], and  
616 incontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole 5%], excessive  
617 salivation [placebo 0%, aripiprazole 4%], and lightheadedness [placebo 1%, aripiprazole  
618 4%].

619 The safety and efficacy of ABILIFY in the treatment of patients with psychosis  
620 associated with dementia have not been established. If the prescriber elects to treat such

621 patients with ABILIFY, vigilance should be exercised, particularly for the emergence of  
622 difficulty swallowing or excessive somnolence, which could predispose to accidental  
623 injury or aspiration. (See also **Boxed WARNING, WARNINGS: Increased Mortality**  
624 **in Elderly Patients with Dementia-Related Psychosis, and Cerebrovascular Adverse**  
625 **Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis.**)

## 626 **Information for Patients**

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

### 629 **Interference with Cognitive and Motor Performance**

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

### 634 **Pregnancy**

635 Patients should be advised to notify their physician if they become pregnant or intend to  
636 become pregnant during therapy with ABILIFY (aripiprazole).

### 637 **Nursing**

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

### 639 **Concomitant Medication**

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

### 642 **Alcohol**

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

644 **Heat Exposure and Dehydration**

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

647 **Sugar Content**

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

650 **Phenylketonurics**

651 Phenylalanine is a component of aspartame. Each ABILIFY DISCMELT orally  
652 disintegrating tablet contains the following amounts: 10 mg - 1.12 mg phenylalanine and  
653 15 mg - 1.68 mg phenylalanine.

654 **Drug-Drug Interactions**

655 Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is  
656 taken in combination with other centrally acting drugs and alcohol. Due to its  $\alpha_1$ -  
657 adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of  
658 certain antihypertensive agents.

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

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

664 Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents  
665 that induce CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole  
666 clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6  
667 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause  
668 increased blood levels.

669 *Ketoconazole:* Coadministration of ketoconazole (200 mg/day for 14 days) with a  
670 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active

671 metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose  
672 (400 mg/day) has not been studied. When concomitant administration of ketoconazole  
673 with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal  
674 dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have  
675 similar effects and need similar dose reductions; weaker inhibitors (erythromycin,  
676 grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from  
677 the combination therapy, aripiprazole dose should then be increased.

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

687 *Carbamazepine:* Coadministration of carbamazepine (200 mg BID), a potent  
688 CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70%  
689 decrease in C<sub>max</sub> and AUC values of both aripiprazole and its active metabolite,  
690 dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole  
691 dose should be doubled. Additional dose increases should be based on clinical evaluation.  
692 When carbamazepine is withdrawn from the combination therapy, aripiprazole dose  
693 should then be reduced.

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

### 697 **Potential for ABILIFY to Affect Other Drugs**

698 Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with  
699 drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day  
700 doses of aripiprazole had no significant effect on metabolism by CYP2D6  
701 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and  
702 CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-

703 aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*  
704 (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**).

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

## 709 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

### 710 **Carcinogenesis**

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

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

733 human risk of the findings of prolactin-mediated endocrine tumors in rodents is  
734 unknown.

### 735 **Mutagenesis**

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

### 746 **Impairment of Fertility**

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

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

### 757 **Pregnancy**

#### 758 **Pregnancy Category C**

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

761 Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and  
762 10 times the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> basis) of  
763 aripiprazole during the period of organogenesis. Gestation was slightly prolonged at  
764 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by  
765 decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal  
766 ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup  
767 survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and  
768 increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at  
769 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence  
770 of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally,  
771 delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive  
772 performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and  
773 increased post-implantation loss, likely mediated through effects on female offspring)  
774 was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was  
775 no evidence to suggest that these developmental effects were secondary to maternal  
776 toxicity.

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

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

788 In pregnant rabbits receiving aripiprazole injection intravenously (3, 10, and 30  
789 mg/kg/day) during the period of organogenesis, the highest dose, which caused  
790 pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal  
791 abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-  
792 effect dose was 10 mg/kg, which produced 15 times the human exposure at the MRHD  
793 based on AUC, and is 6 times the MRHD based on mg/m<sup>2</sup>.

794 In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day  
795 (1, 3, and 10 times the MRHD on a mg/m<sup>2</sup> basis) of aripiprazole perinatally and  
796 postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity  
797 and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and  
798 decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

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

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

## 808 **Labor and Delivery**

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

## 810 **Nursing Mothers**

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

## 814 **Pediatric Use**

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

## 816 **Geriatric Use**

817 Of the 8456 patients treated with oral aripiprazole in clinical trials, 1000 (12%) were ≥65  
818 years old and 794 (9%) were ≥75 years old. The majority (87%) of the 1000 patients  
819 were diagnosed with dementia of the Alzheimer's type.

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

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

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

## 841 **ADVERSE REACTIONS**

842 Aripiprazole has been evaluated for safety in 8456 patients who participated in multiple-  
843 dose, clinical trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's  
844 type, and who had approximately 5635 patient-years of exposure to oral aripiprazole and  
845 749 patients with exposure to aripiprazole injection. A total of 2442 patients were treated  
846 with oral aripiprazole for at least 180 days and 1667 patients treated with oral  
847 aripiprazole had at least 1 year of exposure.

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

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

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

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

## 872 **ORAL ADMINISTRATION**

### 873 **Adverse Findings Observed in Short-Term, Placebo-Controlled** 874 **Trials of Patients with Schizophrenia**

875 The following findings are based on a pool of five placebo-controlled trials (four 4-week  
876 and one 6-week) in which oral aripiprazole was administered in doses ranging from 2 to  
877 30 mg/day.

### 878 **Adverse Events Associated with Discontinuation of Treatment in Short-** 879 **Term, Placebo-Controlled Trials**

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

882 adverse events that led to discontinuation were similar between the aripiprazole and  
883 placebo-treated patients.

### 884 **Commonly Observed Adverse Events in Short-Term, Placebo-** 885 **Controlled Trials of Patients with Schizophrenia**

886 The only commonly observed adverse event associated with the use of aripiprazole in  
887 patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least  
888 twice that for placebo) was akathisia (placebo 4%; aripiprazole 8%).

### 889 **Adverse Findings Observed in Short-Term, Placebo-Controlled** 890 **Trials of Patients with Bipolar Mania**

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

### 893 **Adverse Events Associated with Discontinuation of Treatment in Short-** 894 **Term, Placebo-Controlled Trials**

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

### 899 **Commonly Observed Adverse Events in Short-Term, Placebo-** 900 **Controlled Trials of Patients with Bipolar Mania**

901 Commonly observed adverse events associated with the use of aripiprazole in patients  
902 with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice  
903 that for placebo) are shown in Table 1.

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

| Preferred Term | Percentage of Patients Reporting Event |                    |
|----------------|--|--------------------|
|                | Aripiprazole<br>(n=597)                | Placebo<br>(n=436) |
| Constipation   | 13                                     | 6                  |
| Akathisia      | 15                                     | 3                  |
| Sedation       | 8                                      | 3                  |

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

| Preferred Term          | Percentage of Patients Reporting Event |                    |
|-------------------------|--|--------------------|
|                         | Aripiprazole<br>(n=597)                | Placebo<br>(n=436) |
| Tremor                  | 7                                      | 3                  |
| Restlessness            | 6                                      | 3                  |
| Extrapyramidal Disorder | 5                                      | 2                  |

904

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

908 Table 2 enumerates the pooled incidence, rounded to the nearest percent, of treatment-  
 909 emergent adverse events that occurred during acute therapy (up to 6 weeks in  
 910 schizophrenia and up to 3 weeks in bipolar mania), including only those events that  
 911 occurred in 2% or more of patients treated with aripiprazole (doses  $\geq 2$  mg/day) and for  
 912 which the incidence in patients treated with aripiprazole was greater than the incidence in  
 913 patients treated with placebo in the combined dataset.

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

| System Organ Class<br>Preferred Term                        | Percentage of Patients Reporting Event <sup>a</sup> |                    |
|---|---|--------------------|
|   | Aripiprazole<br>(n=1523)                            | Placebo<br>(n=849) |
| <b>Eye Disorders</b>  |   |                    |
| Vision Blurred  | 3   | 1                  |
| <b>Gastrointestinal Disorders</b>                           |   |                    |
| Nausea  | 16  | 12                 |
| Vomiting  | 12  | 6                  |
| Constipation  | 11  | 7                  |
| Dyspepsia   | 10  | 8                  |
| Dry Mouth   | 5   | 4                  |
| Abdominal Discomfort  | 3   | 2                  |
| Stomach Discomfort  | 3   | 2                  |
| Salivary Hypersecretion                                     | 2   | 1                  |
| <b>General Disorders and Administration Site Conditions</b> |   |                    |
| Fatigue   | 6   | 5                  |
| Pain  | 3   | 2                  |

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

| System Organ Class<br>Preferred Term                    | Percentage of Patients Reporting Event <sup>a</sup> |                    |
|---|---|--------------------|
|   | Aripiprazole<br>(n=1523)                            | Placebo<br>(n=849) |
| Peripheral Edema  | 2   | 1                  |
| <b>Musculoskeletal and Connective Tissue Disorders</b>  |   |                    |
| Arthralgia  | 5   | 4                  |
| Pain in Extremity                                       | 4   | 2                  |
| <b>Nervous System Disorders</b>                         |   |                    |
| Headache  | 30  | 25                 |
| Dizziness   | 11  | 8                  |
| Akathisia   | 10  | 4                  |
| Sedation  | 7   | 4                  |
| Extrapyramidal Disorder                                 | 6   | 4                  |
| Tremor  | 5   | 3                  |
| Somnolence  | 5   | 4                  |
| <b>Psychiatric Disorders</b>                            |   |                    |
| Anxiety   | 20  | 17                 |
| Insomnia  | 19  | 14                 |
| Restlessness  | 5   | 3                  |
| <b>Respiratory, Thoracic, and Mediastinal Disorders</b> |   |                    |
| Pharyngolaryngeal Pain                                  | 4   | 3                  |
| Cough   | 3   | 2                  |
| Nasal Congestion  | 3   | 2                  |
| <b>Vascular Disorders</b>                               |   |                    |
| Hypertension <sup>b</sup>                               | 2   | 1                  |

<sup>a</sup> 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: diarrhea, toothache, upper abdominal pain, abdominal pain, musculoskeletal stiffness, back pain, myalgia, agitation, psychotic disorder, dysmenorrhea<sup>f</sup>, rash.

<sup>b</sup> Including blood pressure increased.

<sup>f</sup> Percentage based on gender total.

914

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

917 **INTRAMUSCULAR ADMINISTRATION**

918 **Adverse Findings Observed in Short-Term, Placebo-Controlled**  
919 **Trials of Patients with Agitation Associated with Schizophrenia**  
920 **or Bipolar Mania**

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

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

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

929 **Commonly Observed Adverse Events in Short-Term, Placebo-**  
930 **Controlled Trials of Patients with Agitation Associated with**  
931 **Schizophrenia or Bipolar Mania**

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

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

940 Table 3 enumerates the pooled incidence, rounded to the nearest percent, of treatment-  
941 emergent adverse events that occurred during acute therapy (24 hour), including only  
942 those events that occurred in 1% or more of patients treated with aripiprazole injection  
943 (doses  $\geq$ 5.25 mg/day) and for which the incidence in patients treated with aripiprazole  
944 injection was greater than the incidence in patients treated with placebo in the combined  
945 dataset.

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

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

<sup>a</sup> 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.

946

947 **Dose-Related Adverse Events**

948 **Schizophrenia**

949 Dose response relationships for the incidence of treatment-emergent adverse events were  
 950 evaluated from four trials in patients with schizophrenia comparing various fixed doses  
 951 (2, 5, 10, 15, 20, and 30 mg/day) of oral aripiprazole to placebo. This analysis, stratified  
 952 by study, indicated that the only adverse event to have a possible dose response  
 953 relationship, and then most prominent only with 30 mg, was somnolence ([including  
 954 sedation] placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

955 **Extrapyramidal Symptoms**

956 In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported  
957 EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients  
958 was 13% vs. 12% for placebo. In the short-term, placebo-controlled trials in  
959 schizophrenia, the incidence of akathisia-related events for aripiprazole-treated patients  
960 was 8% vs. 4% for placebo. In the short-term, placebo-controlled trials in bipolar mania,  
961 the incidence of reported EPS-related events, excluding events related to akathisia, for  
962 aripiprazole-treated patients was 15% vs. 8% for placebo. In the short-term, placebo-  
963 controlled trials in bipolar mania, the incidence of akathisia-related events for  
964 aripiprazole-treated patients was 15% vs. 4% for placebo. Objectively collected data from  
965 those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes  
966 Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for  
967 dyskinesias). In the schizophrenia trials, the objectively collected data did not show a  
968 difference between aripiprazole and placebo, with the exception of the Barnes Akathisia  
969 Scale (aripiprazole, 0.08; placebo, -0.05). In the bipolar mania trials, the Simpson Angus  
970 Rating Scale and the Barnes Akathisia Scale showed a significant difference between  
971 aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25;  
972 placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were  
973 similar for the aripiprazole and placebo groups.

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

978 In the placebo-controlled trials in patients with agitation associated with  
979 schizophrenia or bipolar mania, the incidence of reported EPS-related events excluding  
980 events related to akathisia for aripiprazole-treated patients was 2% vs. 2% for placebo  
981 and the incidence of akathisia-related events for aripiprazole-treated patients was 2% vs.  
982 0% for placebo. Objectively collected data on the Simpson Angus Rating Scale (for EPS)  
983 and the Barnes Akathisia Scale (for akathisia) for all treatment groups, did not show a  
984 difference between aripiprazole and placebo.

985 **Laboratory Test Abnormalities**

986 A between group comparison for 3- to 6-week, placebo-controlled trials revealed no  
987 medically important differences between the aripiprazole and placebo groups in the  
988 proportions of patients experiencing potentially clinically significant changes in routine  
989 serum chemistry, hematology, or urinalysis parameters. Similarly, there were no  
990 aripiprazole/placebo differences in the incidence of discontinuations for changes in serum  
991 chemistry, hematology, or urinalysis.

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

996 **Weight Gain**

997 In 4- to 6- week trials in schizophrenia, there was a slight difference in mean weight gain  
998 between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively), and also a  
999 difference in the proportion of patients meeting a weight gain criterion of  $\geq 7\%$  of body  
1000 weight [aripiprazole (8%) compared to placebo (3%)]. In 3-week trials in mania, the  
1001 mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. -0.2 kg,  
1002 respectively. The proportion of patients meeting a weight gain criterion of  $\geq 7\%$  of body  
1003 weight was aripiprazole (3%) compared to placebo (2%).

1004 Table 4 provides the weight change results from a long-term (26-week), placebo-  
1005 controlled study of aripiprazole, both mean change from baseline and proportions of  
1006 patients meeting a weight gain criterion of  $\geq 7\%$  of body weight relative to baseline,  
1007 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 |
| Mean change from baseline (kg) | -0.5    | -0.5         | -0.6      | -1.3         | -1.5    | -2.1         |
| % with $\geq 7\%$ increase BW  | 3.7%    | 6.8%         | 4.2%      | 5.1%         | 4.1%    | 5.7%         |

1008 Table 5 provides the weight change results from a long-term (52-week) study of  
1009 aripiprazole, both mean change from baseline and proportions of patients meeting a  
1010 weight gain criterion of  $\geq 7\%$  of body weight relative to baseline, categorized by BMI at  
1011 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 $\geq 7\%$ increase BW  | 30%     | 19%       | 8%      |

## 1012 ECG Changes

1013 Between group comparisons for a pooled analysis of placebo-controlled trials in patients  
1014 with schizophrenia or bipolar mania, revealed no significant differences between oral  
1015 aripiprazole and placebo in the proportion of patients experiencing potentially important  
1016 changes in ECG parameters. Aripiprazole was associated with a median increase in heart  
1017 rate of 5 beats per minute compared to a 1 beat per minute increase among placebo  
1018 patients.

1019 In the pooled, placebo-controlled trials in patients with agitation associated with  
1020 schizophrenia or bipolar mania, there were no significant differences between  
1021 aripiprazole injection and placebo in the proportion of patients experiencing potentially  
1022 important changes in ECG parameters, as measured by standard 12-lead ECGs.

## 1023 Additional Findings Observed in Clinical Trials

### 1024 Adverse Events in Long-Term, Double-Blind, Placebo-Controlled Trials

1025 The adverse events reported in a 26-week, double-blind trial comparing oral ABILIFY  
1026 and placebo in patients with schizophrenia were generally consistent with those reported  
1027 in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8%  
1028 (12/153) for ABILIFY vs. 2% (3/153) for placebo]. In this study, the majority of the  
1029 cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in  
1030 therapy (9/12  $\leq 49$  days), and were of limited duration (7/12  $\leq 10$  days). Tremor  
1031 infrequently led to discontinuation ( $< 1\%$ ) of ABILIFY. In addition, in a long-term (52-

1032 week), active-controlled study, the incidence of tremor for ABILIFY was 5% (40/859). A  
1033 similar adverse event profile was observed in a long-term study in bipolar disorder.

## 1034 **Other Adverse Events Observed During the Premarketing** 1035 **Evaluation of Oral Aripiprazole**

1036 Following is a list of MedDRA terms that reflect treatment-emergent adverse events as  
1037 defined in the introduction to the **ADVERSE REACTIONS** section reported by patients  
1038 treated with oral aripiprazole at multiple doses  $\geq 2$  mg/day during any phase of a trial  
1039 within the database of 8456 patients. All reported events are included except those  
1040 already listed in Table 2, or other parts of the **ADVERSE REACTIONS** section, those  
1041 considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so  
1042 general as to be uninformative, events reported with an incidence of  $\leq 0.05\%$  and which  
1043 did not have a substantial probability of being acutely life-threatening, events that are  
1044 otherwise common as background events, and events considered unlikely to be drug  
1045 related. It is important to emphasize that, although the events reported occurred during  
1046 treatment with aripiprazole, they were not necessarily caused by it.

1047 Events are further categorized by MedDRA system organ class and listed in order  
1048 of decreasing frequency according to the following definitions: frequent adverse events  
1049 are those occurring in at least 1/100 patients (only those not already listed in the tabulated  
1050 results from placebo-controlled trials appear in this listing); infrequent adverse events are  
1051 those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than  
1052 1/1000 patients.

1053 *Blood and Lymphatic System Disorders: Infrequent* - anaemia, lymphadenopathy,  
1054 leukopenia (including agranulocytosis, neutropenia); *Rare* - leukocytosis,  
1055 thrombocytopenia, idiopathic thrombocytopenic purpura, thrombocythaemia.

1056 *Cardiac Disorders: Frequent* - tachycardia (including ventricular,  
1057 supraventricular, sinus); *Infrequent* - bradycardia, palpitations, cardiac failure (including  
1058 congestive and acute), myocardial infarction, cardiac arrest, atrial fibrillation,  
1059 atrioventricular block (including first degree and complete), extrasystoles (including  
1060 ventricular and supraventricular), angina pectoris, cyanosis, bundle branch block  
1061 (including left, right), myocardial ischaemia; *Rare* - atrial flutter, cardiomegaly,  
1062 cardiomyopathy, cardiopulmonary failure.

1063            *Ear and Labyrinth Disorders: Infrequent* - ear pain, vertigo, tinnitus; *Rare* -  
1064 deafness.

1065            *Endocrine Disorders: Infrequent* - hypothyroidism; *Rare* - goitre,  
1066 hyperparathyroidism, hyperthyroidism.

1067            *Eye Disorders: Frequent* - conjunctivitis; *Infrequent* - eye redness, eye irritation,  
1068 dry eye, blepharospasm, visual disturbance, eye pain, eye discharge, blepharitis, cataract,  
1069 lacrimation increased; *Rare* - eyelid function disorder, oculogyration, eyelid oedema,  
1070 photophobia, diplopia, eyelid ptosis, eye haemorrhage.

1071            *Gastrointestinal Disorders: Frequent* - loose stools; *Infrequent* - flatulence,  
1072 dysphagia, gastroesophageal reflux disease, gastritis, haemorrhoids, abdominal  
1073 distension, faecal incontinence, haematochezia, gingival pain, rectal haemorrhage,  
1074 abdominal pain lower, oral pain, retching, faecaloma, gastrointestinal haemorrhage, ulcer  
1075 (including gastric, duodenal, peptic), tooth fracture, gingivitis, lip dry; *Rare* - abdominal  
1076 tenderness, chapped lips, periodontitis, apyhalism, gastrointestinal pain, hypoaesthesia  
1077 oral, inguinal hernia, swollen tongue, colitis, haematemesis, hyperchlorhydria, irritable  
1078 bowel syndrome, oesophagitis, faeces hard, gingival bleeding, glossodynia, mouth  
1079 ulceration, reflux oesophagitis, cheilitis, intestinal obstruction, pancreatitis, eructation,  
1080 gastric ulcer haemorrhage, melaena, glossitis, stomatitis.

1081            *General Disorders and Administration Site Conditions: Frequent* - asthenia,  
1082 pyrexia, chest pain, gait disturbance; *Infrequent* - malaise, oedema, influenza-like illness,  
1083 chills, general physical health deterioration, feeling jittery, mobility decreased, thirst,  
1084 feeling cold, difficulty in walking, facial pain, sluggishness, condition aggravated; *Rare* -  
1085 inflammation localized, swelling, energy increased, inflammation, abasia, xerosis, feeling  
1086 hot, hyperthermia, hypothermia.

1087            *Hepatobiliary Disorders: Infrequent* - cholecystitis (including acute and chronic);  
1088 *Rare* - cholelithiasis, hepatitis.

1089            *Immune System Disorders: Infrequent* - hypersensitivity.

1090            *Infections and Infestations: Frequent* - respiratory tract infection (including upper  
1091 and lower), pneumonia; *Infrequent* - cellulitis, dental caries, vaginitis, vaginal infection,  
1092 cystitis, vaginal mycosis, eye infection, gastroenteritis, onychomycosis, vaginal

1093 candidiasis, otitis media, folliculitis, candidiasis, otitis externa, pyelonephritis, rash  
1094 pustular; *Rare* - appendicitis, septic shock.

1095 *Injury, Poisoning, and Procedural Complications: Frequent* - fall, skin laceration,  
1096 contusion, fracture; *Infrequent* - blister, scratch, joint sprain, burn, muscle strain,  
1097 periorbital haematoma, arthropod bite/sting, head injury, sunburn; *Rare* - joint  
1098 dislocation, alcohol poisoning, road traffic accident, self mutilation, eye penetration,  
1099 injury asphyxiation, poisoning, heat exhaustion, heat stroke.

1100 *Investigations: Frequent* - weight decreased, blood creatine phosphokinase  
1101 increased; *Infrequent* - blood glucose increased, heart rate increased, body temperature  
1102 increased, alanine aminotransferase increased, blood cholesterol increased, white blood  
1103 cell count increased, haemoglobin decreased, aspartame aminotransferase increased,  
1104 blood urea increased, electrocardiogram ST segment abnormal (including depression,  
1105 elevation), haematocrit decreased, hepatic enzyme increased, blood bilirubin increased,  
1106 blood glucose decreased, blood creatinine increased, blood alkaline phosphatase  
1107 increased, blood pressure decreased, blood potassium decreased, blood urine present,  
1108 electrocardiogram QT corrected interval prolonged; *Rare* - transaminases increased,  
1109 blood triglycerides increased, blood uric acid increased, cardiac murmur, eosinophil count  
1110 increased, neutrophil count increased, platelet count increased, red blood cell count  
1111 decreased, white blood cell count decreased, white blood cells urine positive, bacteria  
1112 urine identified, blood lactate dehydrogenase increased, blood potassium increased,  
1113 neutrophil count decreased, urine output decreased, blood creatine phosphokinase MB  
1114 increased, ECG signs of myocardial ischemia, electrocardiogram T-wave inversion, heart  
1115 rate decreased, tuberculin test positive, glucose urine present, glycosylated haemoglobin  
1116 increased, glucose tolerance decreased, glycosylated haemoglobin decreased, muscle  
1117 enzyme increased.

1118 *Metabolism and Nutrition Disorders: Frequent* - decreased appetite (including  
1119 diet refusal, markedly reduced dietary intake), dehydration; *Infrequent* - anorexia,  
1120 increased appetite, hypercholesterolaemia, hypokalaemia, hyperglycaemia, diabetes  
1121 mellitus, hypoglycaemia, hyponatremia, diabetes mellitus non-insulin-dependent,  
1122 hyperlipidaemia, obesity (including overweight), polydipsia; *Rare* -  
1123 hypertriglyceridaemia, gout, hypernatraemia, weight fluctuation, diabetes mellitus  
1124 inadequate control.

1125            *Musculoskeletal and Connective Tissue Disorders: Frequent* - musculoskeletal  
1126 pain (including neck, jaw, chest wall, bone, buttock, groin, flank, musculoskeletal chest,  
1127 pubic, and sacral), muscle rigidity, muscle cramp; *Infrequent* - muscle twitching, joint  
1128 swelling, muscle spasms, muscle tightness, arthritis, osteoarthritis, muscular weakness,  
1129 joint range of motion decreased, sensation of heaviness; *Rare* - tendonitis, osteoporosis,  
1130 trismus, arthropathy, bursitis, exostosis, night cramps, coccydynia, joint contracture,  
1131 localised osteoarthritis, osteopenia, rhabdomyolysis, costochondritis, rheumatoid arthritis,  
1132 torticollis.

1133            *Nervous System Disorders: Frequent* - lethargy, dyskinesia; *Infrequent* -  
1134 disturbance in attention, parkinsonism, dystonia, drooling, cogwheel rigidity, dysarthria,  
1135 paraesthesia, hypoaesthesia, loss of consciousness (including depressed level of  
1136 consciousness), hypersomnia, psychomotor hyperactivity, balance disorder,  
1137 cerebrovascular accident, hypokinesia, tardive dyskinesia, memory impairment, amnesia,  
1138 ataxia, dementia, hypotonia, burning sensation, dysgeusia, restless leg syndrome,  
1139 hypertonia, Parkinson's disease, akinesia, dysphasia, transient ischaemic attack, facial  
1140 palsy, hemiparesis, myoclonus, sciatica; *Rare* - bradykinesia, coordination abnormal,  
1141 cognitive disorder, syncope vasovagal, carpal tunnel syndrome, hyporeflexia, intention  
1142 tremor, muscle contractions involuntary, sleep apnea syndrome, dementia Alzheimer's  
1143 type, epilepsy, hyperreflexia, mastication disorder, mental impairment, nerve  
1144 compression, parkinsonian gait, tongue paralysis, aphasia, choreoathetosis, formication,  
1145 masked facies, neuralgia, paresthesia oral, parkinsonian rest tremor, cerebral  
1146 haemorrhage, dizziness exertional, hyperaesthesia, haemorrhage intracranial, ischaemic  
1147 stroke, judgment impaired, subarachnoid haemorrhage.

1148            *Psychiatric Disorders: Frequent* - schizophrenia (including schizoaffective  
1149 disorder), depression (including depressive symptom), hallucination (including auditory,  
1150 visual, tactile, mixed, olfactory, and somatic), mood altered (including depressed,  
1151 euphoric, elevated, and mood swings), paranoia, irritability, suicidal ideation, confusional  
1152 state, aggression, mania, delusion (including persecutory, perception, somatic, and  
1153 grandeur); *Infrequent* - tension, nervousness, nightmare, excitability, panic attack  
1154 (including panic disorder, panic disorder with agoraphobia, and panic reaction), abnormal  
1155 dreams, apathy, libido decreased, hostility, suicide attempt, bipolar disorder (including  
1156 bipolar I), libido increased, anger, delirium, acute psychosis, disorientation, bruxism,  
1157 hypomania, obsessive-compulsive disorder (including obsessive thoughts), mental status  
1158 changes, crying, dysphoria, completed suicide, flat affect, impulsive behaviour; *Rare* -

1159 blunted affect, cognitive deterioration, logorrhea, psychomotor agitation, social avoidant  
1160 behaviour, psychomotor retardation, suspiciousness, affect lability, anorgasmia, fear,  
1161 homicidal ideation, tic, premature ejaculation, dysphemia, bradyphrenia, derealisation,  
1162 depersonalisation.

1163         *Renal and Urinary Disorders: Infrequent* - pollakiuria, dysuria, haematuria,  
1164 urinary retention, renal failure (including acute and chronic), urinary hesitation, enuresis,  
1165 nephrolithiasis, micturition urgency, polyuria; *Rare* - nocturia, proteinuria, glycosuria,  
1166 calculus urinary, azotaemia.

1167         *Reproductive System and Breast Disorders: Infrequent* - erectile dysfunction,  
1168 vaginal discharge, amenorrhoea, vaginal haemorrhage, menstruation irregular,  
1169 menorrhagia, premenstrual syndrome, testicular pain, genital pruritus female, ovarian  
1170 cyst, benign prostatic hyperplasia, prostatitis; *Rare* - gynaecomastia, priapism (including  
1171 spontaneous penile erection), breast pain, pelvic pain, epididymitis, galactorrhoea, uterine  
1172 haemorrhage.

1173         *Respiratory, Thoracic, and Mediastinal Disorders: Frequent* - dyspnoea  
1174 (including exertional); *Infrequent* - sinus congestion, rhinorrhoea, wheezing, epistaxis,  
1175 asthma, hiccups, productive cough, chronic obstructive airways disease (including  
1176 exacerbated), rhinitis allergic, pneumonia aspiration, pulmonary congestion, sinus pain,  
1177 respiratory distress, dry throat, hoarseness; *Rare* - bronchopneumopathy, haemoptysis,  
1178 respiratory arrest, sneezing, hypoxia, pulmonary embolism, pulmonary oedema  
1179 (including acute), respiratory failure, brochospasm, nasal dryness, paranasal sinus  
1180 hypersecretion, pharyngeal erythema, rhonchi, tonsillar hypertrophy, asphyxia,  
1181 Mendelson's syndrome.

1182         *Skin and Subcutaneous Tissue Disorders: Infrequent* - hyperhidrosis, erythema,  
1183 pruritis (including generalised), dry skin, decubitus ulcer, dermatitis (including allergic,  
1184 seborrhoeic, acneiform, exfoliative, bullous, neurodermatitis), ecchymosis, skin ulcer,  
1185 acne, eczema, hyperkeratosis, swelling face, skin discoloration, photosensitivity reaction,  
1186 skin irritation, alopecia, rash maculopapular, cold sweat, scab, face oedema, dermal cyst,  
1187 psoriasis, night sweats, rash erythematous; *Rare* - rash scaly, urticaria, rash  
1188 maculopapular, rosacea, seborrhoea, periorbital oedema, rash vesicular.

1189            *Vascular Disorders: Frequent* - hypotension; *Infrequent* - hot flush (including  
1190 flushing), haematoma, deep vein thrombosis, phlebitis; *Rare* - pallor, petechiae, varicose  
1191 vein, circulatory collapse, haemorrhage, thrombophlebitis, shock.

## 1192    **Other Adverse Events Observed During the Premarketing** 1193    **Evaluation of Aripiprazole Injection**

1194    Following is a list of MedDRA terms that reflect treatment-emergent adverse events as  
1195 defined in the introduction to the **ADVERSE REACTIONS** section reported by patients  
1196 treated with aripiprazole injection at doses  $\geq 1$  mg/day during any phase of a trial within  
1197 the database of 749 patients. All reported events are included except those already listed  
1198 in Table 2 or 3, or other parts of the **ADVERSE REACTIONS** section, those considered  
1199 in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to  
1200 be uninformative, events reported with an incidence of  $\leq 0.05\%$  and which did not have a  
1201 substantial probability of being acutely life-threatening, events that are otherwise  
1202 common as background events, and events considered unlikely to be drug related. It is  
1203 important to emphasize that, although the events reported occurred during treatment with  
1204 aripiprazole injection, they were not necessarily caused by it.

1205            Events are further categorized by MedDRA system organ class and listed in order  
1206 of decreasing frequency according to the following definitions: frequent adverse events  
1207 are those occurring in at least 1/100 patients (only those not already listed in the tabulated  
1208 results from placebo-controlled trials appear in this listing); infrequent adverse events are  
1209 those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than  
1210 1/1000 patients.

1211            *Ear and Labyrinth Disorders: Infrequent* - hyperacusis.

1212            *General Disorders and Administration Site Conditions: Infrequent* - injection site  
1213 stinging, abnormal feeling, injection site pruritus, injection site swelling, venipuncture  
1214 site bruise.

1215            *Infections and Infestations: Infrequent* - bacteruria, urinary tract infection,  
1216 urosepsis.

1217            *Investigations: Infrequent* - blood pressure abnormal, heart rate irregular,  
1218 electrocardiogram T-wave abnormal.

1219 *Psychiatric Disorders: Infrequent* - intentional self-injury.

1220 *Respiratory, Thoracic, and Mediastinal Disorders: Infrequent* -  
1221 pharyngolaryngeal pain, nasal congestion.

1222 *Vascular Disorders: Infrequent* - blood pressure fluctuation.

1223 **Other Events Observed During the Postmarketing Evaluation of**  
1224 **Aripiprazole**

1225 Voluntary reports of adverse events in patients taking aripiprazole that have been  
1226 received since market introduction and not listed above that may have no causal  
1227 relationship with the drug include rare occurrences of allergic reaction (eg, anaphylactic  
1228 reaction, angioedema, laryngospasm, oropharyngeal spasm, pruritis, or urticaria), grand  
1229 mal seizure, and jaundice.

1230 **DRUG ABUSE AND DEPENDENCE**

1231 **Controlled Substance**

1232 ABILIFY (aripiprazole) is not a controlled substance.

1233 **Abuse and Dependence**

1234 Aripiprazole has not been systematically studied in humans for its potential for abuse,  
1235 tolerance, or physical dependence. In physical dependence studies in monkeys,  
1236 withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical  
1237 trials did not reveal any tendency for any drug-seeking behavior, these observations were  
1238 not systematic and it is not possible to predict on the basis of this limited experience the  
1239 extent to which a CNS-active drug will be misused, diverted, and/or abused once  
1240 marketed. Consequently, patients should be evaluated carefully for a history of drug  
1241 abuse, and such patients should be observed closely for signs of ABILIFY misuse or  
1242 abuse (eg, development of tolerance, increases in dose, drug-seeking behavior).

1243 **OVERDOSAGE**

1244 MedDRA terminology has been used to classify the adverse events.

## 1245 **Human Experience**

1246 A total of 76 cases of deliberate or accidental overdose with oral aripiprazole have  
1247 been reported worldwide. These include overdoses with oral aripiprazole alone and in  
1248 combination with other substances. No fatality was reported from these cases. Of the 44  
1249 cases with known outcome, 33 recovered without sequelae and one recovered with  
1250 sequelae (mydriasis and feeling abnormal). The largest known acute ingestion with a  
1251 known outcome involved 1080 mg of oral aripiprazole (36 times the maximum  
1252 recommended daily dose) in a patient who fully recovered. Included in the 76 cases are  
1253 10 cases of deliberate or accidental overdose in children (age 12 and younger)  
1254 involving oral aripiprazole ingestions up to 195 mg with no fatalities.

1255 Common adverse events (reported in at least 5% of all overdose cases) reported  
1256 with oral aripiprazole overdose (alone or in combination with other substances) include  
1257 vomiting, somnolence, and tremor. Other clinically important signs and symptoms  
1258 observed in one or more patients with aripiprazole overdoses (alone or with other  
1259 substances) include acidosis, aggression, aspartate aminotransferase increased, atrial  
1260 fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine  
1261 phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia,  
1262 hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged,  
1263 pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

## 1264 **Management of Overdosage**

1265 No specific information is available on the treatment of overdose with aripiprazole. An  
1266 electrocardiogram should be obtained in case of overdose and, if QTc interval  
1267 prolongation is present, cardiac monitoring should be instituted. Otherwise, management  
1268 of overdose should concentrate on supportive therapy, maintaining an adequate airway,  
1269 oxygenation and ventilation, and management of symptoms. Close medical supervision  
1270 and monitoring should continue until the patient recovers.

1271 *Charcoal:* In the event of an overdose of ABILIFY, an early charcoal  
1272 administration may be useful in partially preventing the absorption of aripiprazole.  
1273 Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of  
1274 aripiprazole, decreased the mean AUC and C<sub>max</sub> of aripiprazole by 50%.

1275 *Hemodialysis:* Although there is no information on the effect of hemodialysis in  
1276 treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose  
1277 management since aripiprazole is highly bound to plasma proteins.

## 1278 **DOSAGE AND ADMINISTRATION**

### 1279 **Oral**

#### 1280 **Schizophrenia**

##### 1281 ***Usual Dose***

1282 The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered  
1283 on a once-a-day schedule without regard to meals. ABILIFY has been systematically  
1284 evaluated and shown to be effective in a dose range of 10 to 30 mg/day, when  
1285 administered as the tablet formulation; however, doses higher than 10 or 15 mg/day were  
1286 not more effective than 10 or 15 mg/day. Dosage increases should not be made before 2  
1287 weeks, the time needed to achieve steady state.

##### 1288 **Dosage in Special Populations**

1289 Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal  
1290 or hepatic impairment status (see **CLINICAL PHARMACOLOGY: Special**  
1291 **Populations**).

1292 *Dosage adjustment for patients taking aripiprazole concomitantly with potential*  
1293 *CYP3A4 inhibitors:* When concomitant administration of ketoconazole with aripiprazole  
1294 occurs, aripiprazole dose should be reduced to one-half of the usual dose. When the  
1295 CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should  
1296 then be increased.

1297 *Dosage adjustment for patients taking aripiprazole concomitantly with potential*  
1298 *CYP2D6 inhibitors:* When concomitant administration of potential CYP2D6 inhibitors  
1299 such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose  
1300 should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is  
1301 withdrawn from the combination therapy, aripiprazole dose should then be increased.

1302           *Dosage adjustment for patients taking potential CYP3A4 inducers:* When a  
1303 potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the  
1304 aripiprazole dose should be doubled (to 20 or 30 mg). Additional dose increases should  
1305 be based on clinical evaluation. When carbamazepine is withdrawn from the combination  
1306 therapy, the aripiprazole dose should be reduced to 10 to 15 mg.

### 1307   **Maintenance Therapy**

1308   While there is no body of evidence available to answer the question of how long a patient  
1309 treated with aripiprazole should remain on it, systematic evaluation of patients with  
1310 schizophrenia who had been symptomatically stable on other antipsychotic medications  
1311 for periods of 3 months or longer, were discontinued from those medications, and were  
1312 then administered ABILIFY 15 mg/day and observed for relapse during a period of up to  
1313 26 weeks, demonstrated a benefit of such maintenance treatment (see **CLINICAL**  
1314 **PHARMACOLOGY: Clinical Studies**). Patients should be periodically reassessed to  
1315 determine the need for maintenance treatment.

### 1316   **Switching from Other Antipsychotics**

1317   There are no systematically collected data to specifically address switching patients with  
1318 schizophrenia from other antipsychotics to ABILIFY or concerning concomitant  
1319 administration with other antipsychotics. While immediate discontinuation of the  
1320 previous antipsychotic treatment may be acceptable for some patients with schizophrenia,  
1321 more gradual discontinuation may be most appropriate for others. In all cases, the period  
1322 of overlapping antipsychotic administration should be minimized.

### 1323   **Bipolar Disorder**

#### 1324    ***Usual Dose***

1325   In clinical trials, the starting dose was 30 mg given once a day. A dose of 30 mg/day was  
1326 found to be effective when administered as the tablet formulation. Approximately 15% of  
1327 patients had their dose decreased to 15 mg based on assessment of tolerability. The safety  
1328 of doses above 30 mg/day has not been evaluated in clinical trials.

1329 **Dosage in Special Populations**

1330 See *Dosage in Special Populations* under **DOSAGE AND ADMINISTRATION:**  
1331 **Schizophrenia.**

1332 **Maintenance Therapy**

1333 While there is no body of evidence available to answer the question of how long a patient  
1334 treated with aripiprazole should remain on it, patients with Bipolar I Disorder who had  
1335 been symptomatically stable on ABILIFY Tablets (15 mg/day or 30 mg/day with a  
1336 starting dose of 30 mg/day) for at least 6 consecutive weeks and then randomized to  
1337 ABILIFY Tablets (15 mg/day or 30 mg/day) or placebo and monitored for relapse,  
1338 demonstrated a benefit of such maintenance treatment (see **CLINICAL**  
1339 **PHARMACOLOGY: Clinical Studies**). While it is generally agreed that  
1340 pharmacological treatment beyond an acute response in mania is desirable, both for  
1341 maintenance of the initial response and for prevention of new manic episodes, there are  
1342 no systematically obtained data to support the use of aripiprazole in such longer-term  
1343 treatment (ie, beyond 6 weeks).

1344 **Oral Solution**

1345 The oral solution can be given on a mg-per-mg basis in place of the 5-, 10-, 15-, or 20-mg  
1346 tablet strengths. Solution doses can be substituted for the tablet doses on a mg-per-mg  
1347 basis up to 25 mg of the tablet. Patients receiving 30-mg tablets should receive 25 mg of  
1348 the solution (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

1349 **Directions for Use of ABILIFY DISCMELT Orally Disintegrating**  
1350 **Tablets**

1351 **Patients should be told the following:**

1352 Do not open the blister until ready to administer. For single tablet removal, open the  
1353 package and peel back the foil on the blister to expose the tablet. Do not push the tablet  
1354 through the foil because this could damage the tablet. Immediately upon opening the  
1355 blister, using dry hands, remove the tablet and place the entire ABILIFY DISCMELT  
1356 orally disintegrating tablet on the tongue. Tablet disintegration occurs rapidly in saliva. It  
1357 is recommended that ABILIFY DISCMELT be taken without liquid. However, if needed,  
1358 it can be taken with liquid. Do not attempt to split the tablet.

1359 **INTRAMUSCULAR INJECTION**

1360 **Agitation Associated with Schizophrenia or Bipolar Mania**

1361 ***Usual Dose***

1362 The efficacy of aripiprazole injection in controlling agitation in these disorders was  
1363 demonstrated in a dose range of 5.25 mg to 15 mg. The recommended dose in these  
1364 patients is 9.75 mg. No additional benefit was demonstrated for 15 mg compared to  
1365 9.75 mg. A lower dose of 5.25 mg may be considered when clinical factors warrant. If  
1366 agitation warranting a second dose persists following the initial dose, cumulative doses  
1367 up to a total of 30 mg/day may be given. However, the efficacy of repeated doses of  
1368 aripiprazole injection in agitated patients has not been systematically evaluated in  
1369 controlled clinical trials. Also, the safety of total daily doses greater than 30 mg or  
1370 injections given more frequently than every 2 hours have not been adequately evaluated  
1371 in clinical trials.

1372 If ongoing aripiprazole therapy is clinically indicated, oral aripiprazole in a range  
1373 of 10 mg to 30 mg/day should replace aripiprazole injection as soon as possible (see  
1374 **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION:**  
1375 **Schizophrenia or Bipolar Disorder**).

1376 ***Administration of ABILIFY Injection***

1377 To administer ABILIFY Injection, draw up the required volume of solution into the  
1378 syringe as shown in Table 6. Discard any unused portion.

**Table 6: ABILIFY Injection Dosing Recommendations**

| <b>Single-Dose</b> | <b>Required Volume of Solution</b> |
|--------------------|------------------------------------|
| 5.25 mg            | 0.7 mL                             |
| 9.75 mg            | 1.3 mL                             |
| 15 mg              | 2 mL                               |

1379 ABILIFY Injection is intended for intramuscular use only. Do not administer  
1380 intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

1381 Parenteral drug products should be inspected visually for particulate matter and  
1382 discoloration prior to administration, whenever solution and container permit.

1383 **Dosage in Special Populations**

1384 See *Dosage in Special Populations* under **DOSAGE AND ADMINISTRATION:**  
1385 **Schizophrenia.**

1386 **ANIMAL TOXICOLOGY**

1387 Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity  
1388 study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and  
1389 60 mg/kg. The 40- and 60-mg/kg doses are 13 and 19 times the maximum recommended  
1390 human dose (MRHD) based on mg/m<sup>2</sup> and 7 to 14 times human exposure at MRHD  
1391 based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal  
1392 evidence of retinal degeneration. Additional studies to further evaluate the mechanism  
1393 have not been performed. The relevance of this finding to human risk is unknown.

1394 **HOW SUPPLIED**

1395 ABILIFY<sup>®</sup> (aripiprazole) Tablets have markings on one side and are available in the  
1396 strengths and packages listed in Table 7.

**Table 7: ABILIFY Tablet Presentations**

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

1397 ABILIFY<sup>®</sup> DISCMELT<sup>™</sup> (aripiprazole) Orally Disintegrating Tablets are round tablets  
 1398 with markings on either side. ABILIFY DISCMELT is available in the strengths and  
 1399 packages listed in Table 8.

**Table 8: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations**

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

1400 ABILIFY<sup>®</sup> (aripiprazole) Oral Solution (1 mg/mL) is supplied in child-resistant bottles  
 1401 along with a calibrated oral dosing cup. ABILIFY oral solution is available as follows:

1402                            150-mL bottle                            NDC 59148-013-15

1403 ABILIFY<sup>®</sup> (aripiprazole) Injection for intramuscular use is available as a ready-to-use,  
 1404 9.75 mg/1.3 mL (7.5 mg/mL) solution in clear, Type 1 glass vials as follows:

1405                            9.75 mg/1.3 mL single-dose vial                            NDC 59148-016-65

1406 **Storage**

1407 **Tablets**

1408 Store at 25° C (77° F); excursions permitted between 15° C to 30° C (59° F to 86° F) [see  
 1409 USP Controlled Room Temperature].

1410 **Oral Solution**

1411 Store at 25° C (77° F); excursions permitted between 15° C to 30° C (59° F to 86° F) [see  
 1412 USP Controlled Room Temperature]. Opened bottles of ABILIFY oral solution can be  
 1413 used for up to 6 months after opening, but not beyond the expiration date on the bottle.  
 1414 The bottle and its contents should be discarded after the expiration date.

1415 **Injection**

1416 Store at 25° C (77° F); excursions permitted between 15° C to 30° C (59° F to 86° F) [see  
1417 USP Controlled Room Temperature]. Protect from light by storing in the original  
1418 container. Retain in carton until time of use.

1419 Tablets manufactured by Otsuka Pharmaceutical Co, Ltd, Tokyo, 101-8535 Japan or  
1420 Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

1421 Orally disintegrating tablets, Oral solution and Injection manufactured by Bristol-Myers  
1422 Squibb Company, Princeton, NJ 08543 USA

1423 Distributed and marketed by Otsuka America Pharmaceutical, Inc, Rockville, MD 20850  
1424 USA

1425 Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

1426 US Patent Nos: 5,006,528; 6,977,257; and 7,115,587



**Bristol-Myers Squibb Company**



**Otsuka America Pharmaceutical, Inc.**

1427 1216978A1 1191707A7 1170/10-06

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